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NETWORK BIOLOGY APPROACH TO IDENTIFY MOLECULAR ASSOCIATION BETWEEN ATOPIC DERMATITIS AND INFLAMMATORY BOWEL DISEASE

Tammanna R. Sahrawat*, Ras Preeti Sharma

Centre for Systems Biology and Bioinformatics, UIEAST, Panjab University, Chandigarh, India.

ABSTRACT: Atopic dermatitis is a skin condition that leaves people with persistent itching, redness, and rashes. Mostly occurs in children, but can persist into adulthood. It results from environmental triggers, genetic factors, and immune dysfunction, interfering with the skin's barrier. In contrast, inflammatory bowel disease primarily affects the digestive system, causing diarrhea, stomach issues, and fatigue due to an overactive immune response. Although both conditions are different, recent clinical studies have suggested a significant relationship between them. Therefore, using a network-based system biology approach, present study investigates the molecular link between AD and IBD. Microarray datasets for AD and IBD, were retrieved from GEO database, followed by identification of DEGs using GEO2R, focusing on the overlapping dysregulated genes. A PPI network was built using STRING, and network visualization, along with topology analysis, was done using Cytoscape plug-ins, followed by enrichment analysis using ExpressAnalyst. 102 common DEGs between the two diseases were found, with CXCL8, CXCL10, CXCL1, MMP9, STAT1, CXCL9, MMP3, and MMP1 identified as key hub genes. Enrichment analysis indicated their participation in signaling pathways, highlighting their role in immune responses. This study highlights common hub genes that could be used as therapeutic targets by exposing shared molecular processes between AD and IBD. These results provide encouraging clues for further research and experimental validation.

Keywords: Atopic Dermatitis, Inflammatory Bowel Disease, Chemokine, Microarray.

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Corresponding Author: Dr. Tammanna R. Sahrawat* PhD.

Centre for Systems Biology and Bioinformatics, UIEAST, Panjab University, Chandigarh, India.

Email Address: tammanna@pu.ac.in

1. INTRODUCTION

Atopic dermatitis (AD) is a skin disorder which is characterized by dry, cracked, red or brownish, scaly skin and intensely itchy skin, along with eczema flares and disease exacerbations. Approximately 10-20% of children and 2-10% of adult population gets affected by AD, putting significant economic burdens on both healthcare facilities and individual lives [1,2]. The pathophysiology of AD is complicated and multifactorial, with factors like a weakened skin barrier, genetic susceptibility, immunological dysregulation, and psycho-neurogenic inflammation [3,4]. Although AD was initially considered an allergic skin condition, it is now characterised as a more complex disorder with extreme clinical manifestations [5]. Additionally, studies have also highlighted the relation between AD and various systemic conditions, such as ophthalmologic abnormalities, inflammatory bowel disease (IBD), and autoimmune disorders [6]. Inflammatory bowel disease is an idiopathic, prolonged, episodic inflammatory disorder of the gastrointestinal system characterized by recurrent and intermittent inflammation of the intestine that are associated with low quality of life [7]. Two most common symptoms of IBD are Crohn's disease and Ulcerative colitis [8]. Clinical and experimental studies reported that occurrence and progression of IBD are affected by multiple factors such as environmental, immunological, genetic, and infectious elements. IBD includes a range of symptoms, from mild to severe, and also includes abdominal discomfort, vomiting, diarrhea, weight loss, internal rectal bleeding, muscle spasm, fever, and gastrointestinal bleeding [9]. Despite the comprehensive research, proper cause and development of human IBD remains unclear. Although AD and IBD are considered distinct, some recent evidence suggests their association *via* shared underlying immune and genetic mechanisms [10]. A study by Tian *et al.*, 2024 provided a detailed analysis of AD immune processes, highlighting increased levels of factors such as interleukin 4 (IL-4), IL-13, IL-4 Receptor, IL-33, and thymic stromal lymphopoietin [2]. Neutrophils, on the other hand, also play a critical role in the initial immune responses to tissue damage in IBD patients, releasing proinflammatory cytokines and chemokines that recruit other immune cells, enhancing the inflammatory response. These cytokine imbalances and immune response mechanisms in IBD may also share similarities with AD, suggesting that potential overlap between pathways could explain why AD patients may be at a higher risk of developing IBD [11,12]. Epidemiological studies have suggested a potential relation between AD and IBD, supported by the results of case-control and cohort studies on IBD patients and a systematic review [13,14]. Further supporting the link between AD and IBD, recent genetic studies have identified potential biomarkers linked to each condition individually. Yaguang Zhou *et al.*, 2024 reported seven key hub genes related to AD, having high diagnostic specificity and sensitivity: CCL2, CCL22, GZMB, IL7R, CCR7, CD274, and IRF7, suggesting these hub genes as potential therapeutic biomarkers of AD [15]. Similarly, a study conducted for IBD examined differential expression in IBD-related epithelial barrier genes, and MUC1, MUC4, MAGI1, CLDN1, CLDN8, OCLN, DSG3, and TFF1 were

identified as potential biomarkers [16]. While previous studies have investigated key genes or biomarkers linked to AD or IBD individually, as well as using meta-analyses of genome-wide association studies to explore their genetic correlations, the molecular mechanisms underlying the co-occurrence of AD and IBD remain poorly understood. Therefore, the present study was undertaken to investigate the shared genes and pathways between AD and IBD.

2. MATERIALS AND METHODS

2.1 Data Retrieval and Identification of Differentially Expressed Genes

GEO was used to retrieve the microarray datasets of AD and IBD and were analysed to understand and compare transcriptomic profiles of AD and IBD. Dataset GSE32924, contained skin samples of 13 AD patients and 8 healthy controls [17]. For IBD, GSE75214 dataset was selected that included mucosal samples collected from ileum of 67 patients with Crohn's disease (CD) and 11 non-IBD controls, along with samples taken from colon of 97 ulcerative colitis (UC) patients, 8 CD patients, and 11 control subjects [18]. A differential analysis was performed using GEO2R between disease and control samples of AD and IBD to identify the DEGs. Significantly dysregulated genes were analyzed using criteria of $p < 0.05$, and log2 FC of ± 1 [19,20]. The overlapping DEGs between AD and IBD were visualized by constructing a Venn diagram with IntractiVenn [21].

2.2 PPI Network Construction and Identification of Hub Genes

To build a PPI network of the common DEGs, STRING database was used, with confidence score set to high (>0.7). Further the obtained PPI network was analysed using Cytoscape's multiple plug-ins: CytoHubba, ClusterMaker, and Network Analyzer [22,23]. ClusterMaker was used to identify interconnected clusters in the primary network [24]. This was followed by detection of hub genes within the significant clusters using CytoHubba plugin, where darker node colors indicated higher importance in the interaction network based on topological properties [25]. Finally, these hub genes were validated using Network Analyzer, where nodes with a higher degree, based on the number of edges, were regarded as hub genes [26].

2.3 KEGG Enrichment of Hub Genes

To identify the potential molecular pathways hub genes are involved in KEGG [Kyoto Encyclopedia of Genes and Genomes] enrichment was performed using ExpressAnalyst [27].

3. RESULTS AND DISCUSSION

3.1 Data Retrieval and Identification of DEGs

GEO2R was used to perform bioinformatics analysis on the GSE32924 dataset for AD, which screened a total of 1,980 DEGs, consisting of 801 upregulated and 1,197 downregulated genes. Similarly, the GSE75214 dataset for IBD identified 525 DEGs, which includes 212 upregulated and 313 downregulated. These results were visualized in the volcano plots (Figure 1a, 1b), followed by a cross-section analysis of dysregulated genes using InteractiVenn that revealed a total of 102 DEGs common between AD and IBD (Figure 1c).

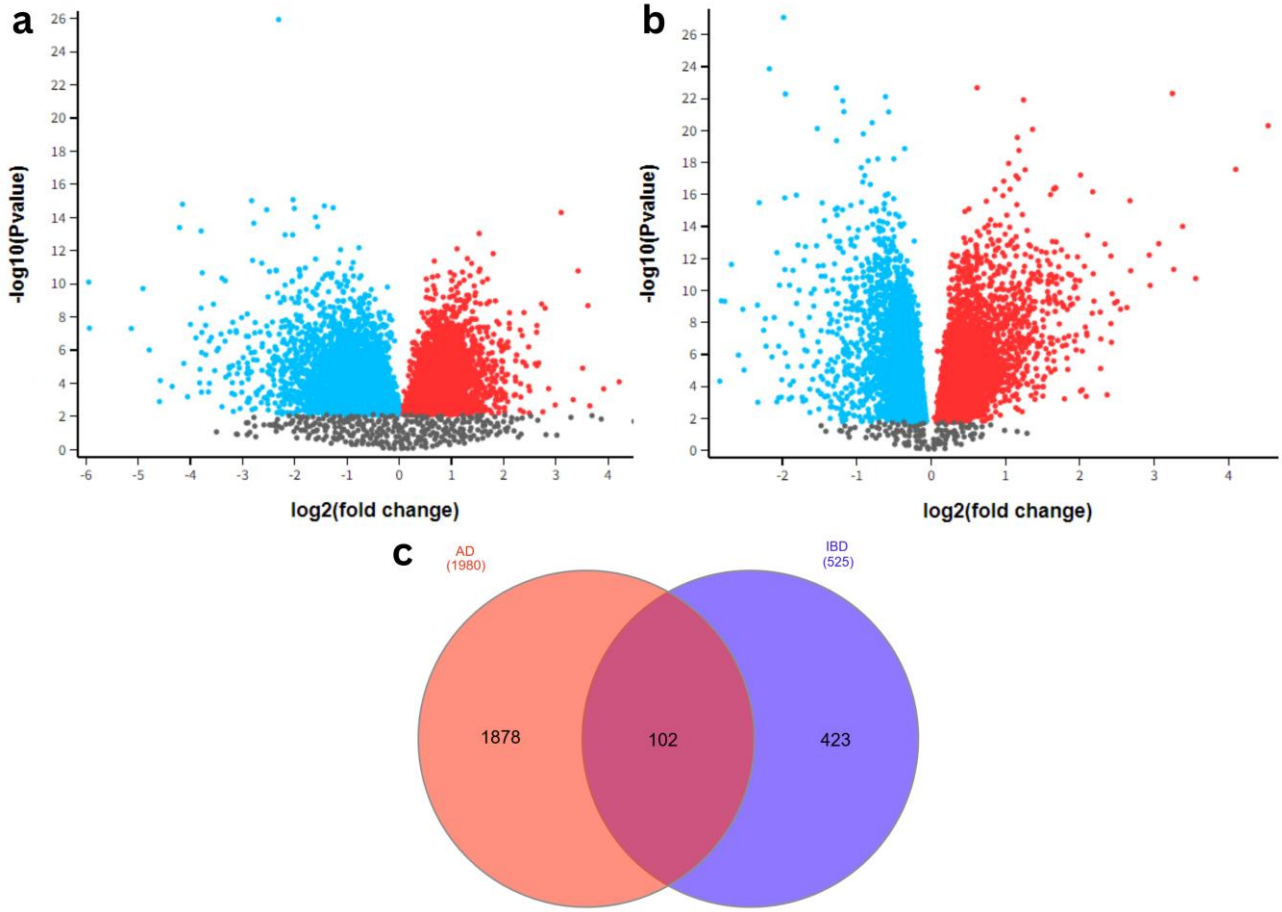

Figure 1: Volcano plots of the (a) GSE32924 and (b) GSE75214 datasets. The x-axis represents log2 (fold change) and the y-axis represents − log10 (P value). Red dots indicate up-regulated genes and blue dots indicate down-regulated genes. (c) Venn Diagram of common DEGs in both GSE32924 and GSE75214 datasets.

3.2 PPI Network Construction and Analysis

PPI network of 102 common DEGs was constructed to identify the interactions using the STRING database (Figure 2a), and the network contains 101 nodes, which represent genes, and 108 edges, which represent gene-to-gene interactions, was obtained. The resulting network was analyzed in Cytoscape using ClusterMaker with Markov Clustering (MCL) algorithm and CytoHubba that uses Maximum Clique Centrality (MCC) algorithm for ranking the highest interacting genes (Figure 2b, Table 1). Further validation was done using Network Analyzer plug-in, which identifies hub genes based on degree centrality (Figure 2c, Table 1). From a cross-comparison between the highly significant genes using various Cytoscape plug-ins, eight key hub genes, namely CXCL8, CXCL10, CXCL1, MMP9, STAT1, CXCL9, MMP3, and MMP1, for the molecular association of AD and IBD were identified.

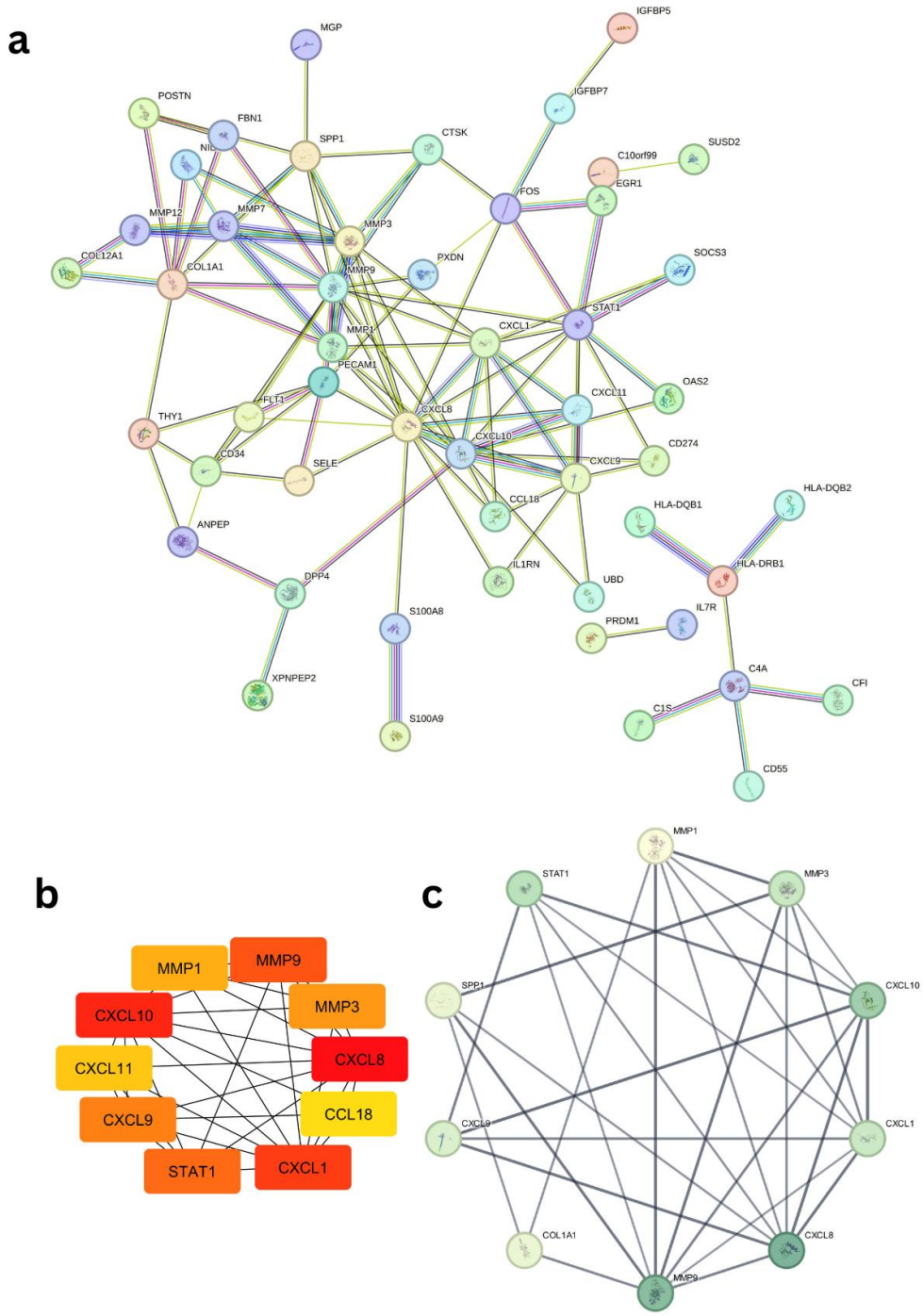

Figure 2: Protein-protein interaction (PPI) network constructed using STRING (a). The hub genes were screened from the PPI network using the (b) ClusterMaker and (c) Network Analyzer

Table 1. Top 10 hub genes ranked based on ClusterMaker (MCL), MCC algorithm of CytoHubba, and degree-based Network Analyzer in Cytoscape.

CytoHubba			Network Analyzer	
Score	Genes	Rank	Genes	Degree
306	CXCL8	1	CXCL8	16
299	CXCL10	2	MMP9	15
290	CXCL1	3	CXCL10	13
188	MMP9	4	STAT1	11
158	STAT1	5	MMP3	10
154	CXCL9	6	CXCL1	10
148	MMP3	7	CXCL9	9
128	MMP1	8	SPP1	8
120	CXCL11	9	COL1A1	8
24	CCL18	10	MMP1	7

3.3 KEGG Pathway Analysis of Hub Genes

The KEGG pathway analysis of identified hub genes revealed them to be enriched in pathways of Toll-like receptor signaling, IL-17 signaling, and chemokine signaling pathway emerged as significant, highlighting their role in immune responses (Figure 3).

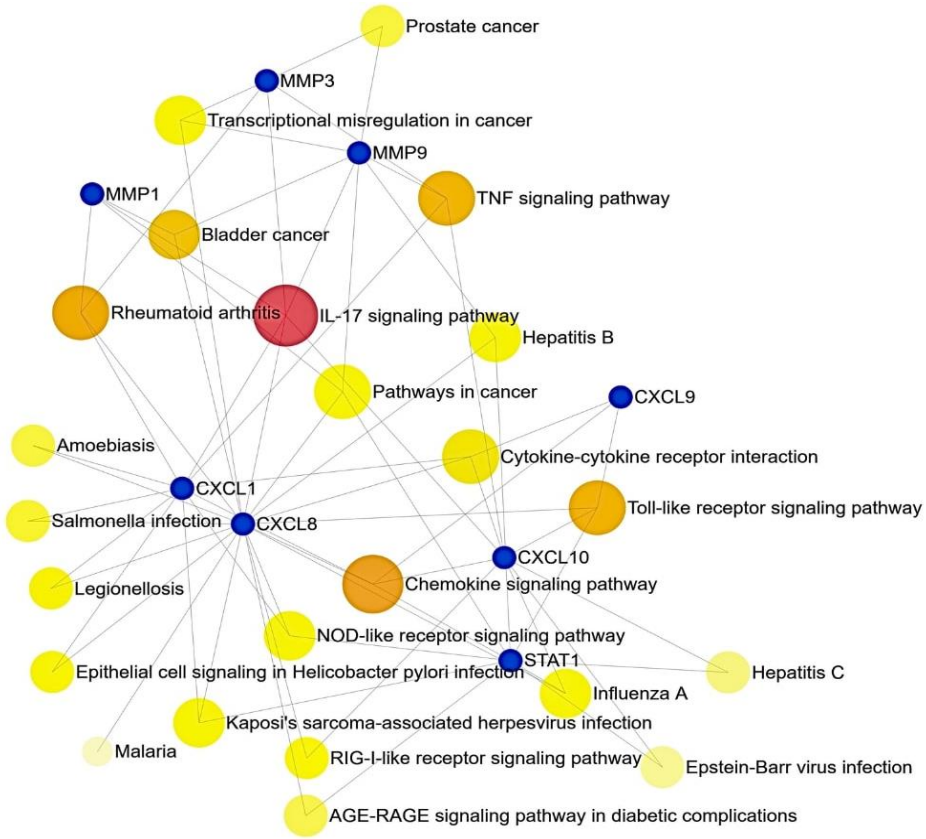

Figure 3: KEGG Pathway Analysis of Top 8 Hub Genes.

DISCUSSION

The present study was conducted to identify the relation between AD and IBD at the molecular level, and identified eight hub genes, all of which were found to be involved in the immune-related pathways. The hub genes CXCL8, CXCL10, CXCL1, and CXCL9 identified are from the CXC chemokine protein family, which play a crucial role in directing immune cell trafficking to sites of infection or inflammation. CXCL8 overexpression has been strongly associated with the key inflammatory processes. A recent study by Yu JE *et al.,* 2024 demonstrated the CXCL8 collaboration with the factors like CHI3L1 to influence skin inflammation in the AD model [28]. In IBD patients, CXCL8 is differentially expressed, with its up-regulation in blood samples of Ulcerative colitis patients and down-regulation in Crohn's disease patients [29,30]. Studies by Hashimoto *et al.*, 2018 and Walsh *et al.,* 2019 revealed that CXCL10, released by skin epithelial cells and neutrophils, promotes itching and inflammation *via* the CXCR3 receptor, along with research on mice suggesting increased levels of CXCL10 in AD patients [31,32]. Similarly, in the case of IBD, the severity is correlated with the CXCL10 high concentration in serum and intestinal mucosa of those patients [32,33]. In a study, Huibin Yin *et al.,* 2020 suggested that, along with CXCL10, CXCL9 also contributes to the inflammation and skin barrier disruption, with high concentration suggesting a role in the progression of AD by influencing inflammatory and immune pathways [34]. The CXCL9 overexpression in IBD patients has also been reported, suggesting its role in inflammation and fibrosis, particularly with anti-TNF therapy resistance [35]. CXCL1 recruits neutrophils to inflamed skin in AD patients, has been reported to often work alongside other factors like CXCL8 to deepen the immune response and worsen skin lesions [36,37]. Recent studies have reported that elevated levels of CXCL1 and CXCL10 correlate with more critical inflammatory lesions and contribute to impacting sensory neurons [36]. A study by Liu H.Y. *et al.*, 2025 suggested that elevated CXCL1 production by macrophages resulting from disruption of IL-10 signaling leads to exacerbating conditions like colitis [38]. Furthermore, IBD patients, particularly those with unresponsive to standard therapies, have neutrophils that are hyper-responsive and produce a huge amount of CXCL1, contributing to the severity of the disease [39]. MMP1, MMP3, and MMP9 are all members of the Matrix metalloproteinase family, and were identified in this study as hub genes, which play an important role in the degradation of the Extracellular matrix (ECM). In AD patients, the upregulation of MMP1 is reported in both lesional skin and non-lesional skin, corresponding to the intestinal collagens type I and III degradation, causing irritation and pathogenesis as the degradation weakens the skin barrier and therefore worsens inflammation and symptoms of itching, redness, and dry patches on the skin [40–42]. In contrast with IBD patients, MMP1 has been reported to be upregulated in inflamed mucosa, breaking down the intestinal epithelium's ECM and contributing to barrier dysfunction [43,44]. MMP1 also interacts with other matrix metalloproteinases, such as MMP9 and MMP8, influencing immune cell infiltration and continuing the cycle of inflammation

and tissue destruction [45]. MMP3 has also been reported to be involved in the degradation of interstitial collagens (types I and III), influencing skin barrier weakening and dysfunction, leading to worsening inflammatory responses. Wang J. *et al.,* 2024 recently reported that elevated levels of MMP3 in serum sample of AD patients influence increased pro-inflammatory cytokine activity [46]. Studies have shown that IBD patients with elevated MMP3 levels correlate with increased pro-inflammatory cytokine activity [47]. Increased levels of MMP9 were found in both chronic and acute AD lesions, facilitating immune cell infiltration, further contributing to tissue damage and cleaving proinflammatory chemokines, thereby enhancing the inflammation and sustaining the conditions [48]. Furthermore, elevated levels of MMP9 expression have been reported in the inflamed colonic mucosa, urine, faecal, and serum samples of IBD patients, which corresponds to inflammation severity and tissue remodelling [49]. Studies have also suggested that long non-coding RNAs (lncRNAs) also affect the MMP9 expression, highlighting it as a potential therapeutic target [50]. STAT1 (Signal transducer and activator of transcription 1-alpha/beta), a critical mediator in cellular responses to various cytokines and interferons, participates in the inflammatory response. In a study, Boriero *et al.*, 2021 suggested that STAT2 phosphorylation, inhibited by compounds like Myricetin, reduces production of Th2 cytokines and contributes to skin barrier repair, making STAT1 a potential therapeutic target for AD [51]. In IBD patients, elevated levels of STAT1 and p-STAT1 have also been reported, which directly influence pro-inflammatory genes TNFAIP2 and LCP2 via H3K27ac enrichment at their enhancers [52]. The identified hub genes, namely CXCL1, CXCL8, CXCL9, CXCL10, MMP1, MMP3, MMP9, and STAT1, have been previously reported individually in AD or IBD; however, to our knowledge, this report is first of its kind that provides an understanding of critical molecular foundation of common genes and pathways in both diseases. Our findings indicate shared inflammatory pathways in AD and IBD, paving the way for therapeutic strategies that could address both diseases. A limitation of this study is that the identified genes have not been validated through experimental or clinical research, which could provide valuable insights for developing common therapeutic strategies for both diseases.

4. CONCLUSION

This study is one of the first to use a network-based systems biology approach to investigate the molecular relationship between AD and IBD. Eight genes, namely CXCL8, CXCL10, CXCL1, MMP9, STAT1, CXCL9, MMP3, and MMP1, were identified as common hub genes that may play critical roles in the co-occurrence of these conditions. Their importance in immunological responses was highlighted by enrichment analysis, which showed their involvement in pathways like Toll-like receptor, chemokine, and IL-17 signaling. These findings suggest that the hub genes and pathways that have been identified may be used as therapeutic targets as well as possible biomarkers for diagnosis and prognosis. Further clinical or experimental researches are needed to confirm their involvement and explore novel strategies to reduce the advancement of the diseases.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals or humans were used for the studies that are based on this research.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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