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Differential Gene Expression Profiles in Inflammatory Bowel Disease Patients from Kurdistan, Iraq

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Abstract

***Objectives*:** Inflammatory bowel disease, generally comprising Crohn's disease (CD) and ulcerative colitis (UC), has become a significant global public health concern in the last decade. The present study aimed to determine the alterations of the whole genomic expression profile among patients with inflammatory bowel disease. This study was conducted to provide the expression profile of IBD patients for the first time in this geographic location, as there are very few articles in the literature addressing this specific aspect. ***Methods*:** A study conducted in Erbil province, Kurdistan region of Iraq, from July 2021 to July 2022 compared the genome expression profiles of 10 patients with inflammatory bowel diseases to their matched controls. The sequences used in the design of this array were selected from GenBank®, dbEST, and RefSeq, Whole blood RNA extracted and hybridization on GeneChip® human genome U133A 2.0. The Scanner 3000 was used for the scanning high-resolution image and operating software (GCOS) was used for reading the results. ***Results*:** Shared upregulated genes between ulcerative colitis (UC) and Crohn's disease (CD) were (*RIT2*, *BCL2L1*, *MDM2*, and *FKBP8*) while shared downregulated genes were (*NFKBIB*, *DDX24*, and *RASA3*). ***Conclusions*:** Upregulated and downregulated gene expression patterns are detected in individuals with inflammatory bowel disease, offering diagnostic potential and opportunities for treatment by targeting the associated pathways.

Keywords: Crohn's disease, Expression, Erbil, Gene, Ulcerative colitis.

Advances in Knowledge:

1. The study determines the alterations of the whole genomic expression profile in patients with inflammatory bowel disease (IBD).
2. Genes (*RIT2*, *BCL2L1*, *MDM2*, *FKBP8*) were found to be upregulated in both ulcerative colitis (UC) and Crohn's disease (CD), while genes (*NFKBIB, DDX24, RASA3*) were downregulated.
3. These findings contribute to understanding the molecular basis of IBD and provide potential diagnostic markers.
4. Identification of shared differentially expressed genes offers insights into common mechanisms underlying UC and CD pathogenesis.
5. The study highlights the importance of genomic alterations as potential targets for future treatments.

Application to Patient Care:

1. The observed alterations in gene expression among IBD patients have significant implications for diagnosis and treatment.
2. The identified upregulated genes (*RIT2, BCL2L1, MDM2, FKBP8)* and downregulated genes (*NFKBIB, DDX24, RASA3*) can serve as potential biomarkers for IBD.
3. Targeting the pathways associated with these differentially expressed genes may lead to the development of novel therapeutic interventions.
4. The findings provide a basis for personalized medicine approaches in IBD, allowing for tailored treatments based on individual genomic profiles.
5. Understanding the molecular changes in IBD enhances the potential for precision medicine and improved patient care.

Introduction

Inflammatory bowel disease (IBD) is a group of gastrointestinal disorders that clinically includes Crohn's disease (CD), ulcerative colitis (UC), and other indeterminate colitis. [1] Over the past decade, IBD has emerged as a global public health challenge. [2] The incidence pattern of IBD has

shifted during the past 20 years, increasing incidence in previously low incidence regions like Asia and the Middle East as well as continuing to rise in the West. [3] Inflammatory bowel disease (IBD) is a complex and heterogeneous group of disorders that exhibit significant geographic and ethnic variations in both incidence and prevalence. [4] These differences underscore the importance of understanding the molecular underpinnings of IBD within specific populations.[5] While numerous studies have explored the clinical aspects of IBD, there is a growing need to investigate the underlying genetic and genomic factors contributing to the disease's pathogenesis.

The pathogenesis of IBD are not known; however, it is considered to be multifactorial and a cure for IBD has yet to be discovered. [6] Recent experimental and clinical studies, agreed that genetics, environment, gut microbiota and immune response are responsible for the initiation and progression of IBD in susceptible host. [7] Additionally, it has been proposed that diet, lifestyle and pollutants and the deficiency of (vitamins and minerals) contribute to the severity or the development of IBD. [8], and [9] Previously, the deficiency of micronutrients observed in IBD patients, for instance, high prevalence of vitamin deficiency reported among patients with IBD including vitamin D, C, B12, folic acid and zinc. [10]

Experimental study revealed that the invasion of mucosal tissue with activated phagocytic immune cells that produce reactive oxygen and nitrogen species (ROS and RNS, respectively), lead a change towards prooxidants and hence increases of oxidative stress, which disrupts cellular homeostasis by injuring important macromolecules, leads to cell damage, increases mucosal barrier permeability, and increases locally existing inflammation. [11] and [12] Thus, oxidative stress has been mentioned as a potential contributor to the etiology of IBD. [12] The level oxidative stress can be evaluated indirectly by assessing the quantities of DNA/RNA damage, lipid peroxidation, and protein oxidation/nitration. [13] Lipids are the most involved class of macromolecules among the numerous biological targets of oxidative stress. [14] Malondialdehyde (MDA), is one of the final products of polyunsaturated fatty acids peroxidation which also well-known oxidative stress biomarker, it is overproductions related to increase of free radicals and decrease the levels of antioxidants. [15]

Materials and Methods

This study conducted in Erbil province - Kurdistan region of Iraq, from July 2021 to July 2022. In this experiment, the genome expression profile of patients with UC (6) and CD (4) determined and compared to their matched controls (5). The criteria for the diagnosis of IBD was a combination of clinical, radiographic, histological and endoscopic assessment and the collected data were reviewed by 3 independent physicians, while exclusion criteria were colitis from other cause. Additionally, anyone who had any of the following criteria were disqualified: pregnant women, nursing mothers, people who had undergone a total colectomy in the past, people who were taking experimental medications, people who had cancer or any other concurrent end-stage organ disease, and addicts. All conscripts who were not given an IBD diagnosis were considered to be part of the control population. Ethical approval for this study was obtained from the Salahaddin University College of Science. The study adhered to all ethical guidelines and regulations regarding the treatment of human subjects. Official permission was obtained to collect samples from patients involved in the study. Prior to their inclusion, all patients provided written informed consent, detailing the purpose of the research, potential risks and benefits, and their rights as participants. Participant confidentiality was strictly maintained throughout the study.

The collected samples were peripheral blood RNA extracted from blood samples and hybridization on GeneChip® human genome U133A 2.0 array. This array well designed to analyzes the expression level of 18,400 transcripts and variants, including 14,500 well-characterized human genes. The sequences used in the design of this array were selected from GenBank®, dbEST, and RefSeq. The sequence clusters were created from the UniGene database (Build 133, April 20, 2001) and then refined by analysis and comparison with a number of other publicly available databases, including the Washington University EST trace repository and the University of California, Santa Cruz Golden-Path human genome database (April 2001 release). Oligonucleotide probes complementary to each corresponding sequence are synthesized in situ on the array. Eleven pairs of oligonucleotide probes are used to measure the level of transcription of each sequence represented on this array. The Scanner 3000 was used for the scanning high-resolution image and operating software (GCOS) was used for reading the results. Bioinformatic

analysis started with preprocessing (normalization and scatter plots), alignment conducted for assemble transcripts, statistical tool ANOVA used to determine the top upregulated and downregulated genes, heat map created with TBtools, g:Convert used for the conversion of gene numbers to gene IDs, co-expression of related genes identified with Genemania-online tools, and finally ShinyGO 0.76.3 tool used for the determining the defected pathways related to upregulated and downregulated genes.

All of the statistical analyses were performed in SPSS version 25 (IBM Corp., Armonk, NY, USA) and p-values of < 0.05 were considered to indicate statistical significance. ANOVA were used for determining the fold changes in each gene.

Results

Figure (1) shows the list of up regulated genes and figure (2) shows the list of downregulated genes in UC. Top upregulated genes and downregulated genes in CD presented in Figure (3) and (4), respectively. The following genes downregulated in UC (*RNF19A, NFKBIB, EWSR1, DDX24, HES2, SART3, PPIG, TCAF1, DKC1, RASA3, CELF1, CCL23, SNRNP70, MXD4, CD6, HSP90AA1, PPIG, DNAJB4*). Conversely, the downregulated genes in patients with CD were (*ZCCHC24, ILF3, RASA3, LAMB1, TRABD, TNFRSF25, BDH1, MAF, PIN1, GDPD5, PBXIP1, PRPF6, AP3D1, DDX24, DIO2, GGA1, CORO1B, NFKBIB*). Significantly upregulated genes in patients with UC were (*MDM2, SLC6A2, TRMT1, SNCA, CYP4B1, TNS1, RIT2, ZER1, SLC4A1, GNGT1, FOXH1, FKBP8, TNS1, CA1, TMOD1, SELENBP1, ALAS2, BCL2L1*). Conversely, upregulated genes in patients with CD were (*CXCL1, MDM2, GUCY1B3, DZIP1, RIT2, GYPA, FECH, PIGV, SHOX2, SARDH, DOHH, NR4A1, FKBP8, CXCL3, NFIX, MIA, ABLIM3, BCL2L1*).

The pathways of shared upregulated genes (*RIT2, BCL2L1, MDM2,* and *FKBP8*) and downregulated genes (*NFKBIB, DDX24,* and *RASA3*) in IBD identified, we found that *BCL2L1* and *MDM2* have roles in the following pathways (p53 signaling pathway and NF-κB signaling pathway), respectively. The *NFKBIB* related to the cytosolic DNA-sensing pathway, adipocytokine signaling pathway, B cell receptor signaling pathway, and chemokine signaling

pathway, and *RASA3* related to the (Ras signaling pathway). Also, we found that *DDX24* has a role in controlling p53 activities.

Discussion

To date, there are no published DNA microarray-based studies in Kurdistan region of Iraq and even there are small number of such studies in Middle-East based on DNA microarray to investigate the changes of gene expression in patients with IBD. Thus, in the present study the expression of the genes investigated via DNA microarray. For this purpose, blood mRNA was collected from 10 patients with IBD (6 patients with UC and 4 patients with CD) and 5 controls, the enrolled patients and controls were from Kurdistan region of Iraq. the results of the present study explained through online and offline bioinformatic tools such as (Tbtools) for drawing the heatmap, (Genemania) for determining the co-expression of the genes, (G:GOSt) for converting gene names to Ensemble IDs, and (STRING) for finding gene interactions and pathways. The top upregulated and downregulated genes in both UC and CD determined regarding the control group. The following genes downregulated in UC (*RNF19A, NFKBIB, EWSR1, DDX24, HES2, SART3, PPIG, TCAF1, DKC1, RASA3, CELF1, CCL23, SNRNP70, MXD4, CD6, HSP90AA1, PPIG, DNAJB4*). Conversely, the downregulated genes in patients with CD were (*ZCCHC24, ILF3, RASA3, LAMB1, TRABD, TNFRSF25, BDH1, MAF, PIN1, GDPD5, PBXIP1, PRPF6, AP3D1, DDX24, DIO2, GGA1, CORO1B, NFKBIB*). Significantly upregulated genes in patients with UC were (*MDM2, SLC6A2, TRMT1, SNCA, CYP4B1, TNS1, RIT2, ZER1, SLC4A1, GNGT1, FOXH1, FKBP8, TNS1, CA1, TMOD1, SELENBP1, ALAS2, BCL2L1*). Conversely, upregulated genes in patients with CD were (*CXCL1, MDM2, GUCY1B3, DZIP1, RIT2, GYPA, FECH, PIGV, SHOX2, SARDH, DOHH, NR4A1, FKBP8, CXCL3, NFIX, MIA, ABLIM3, BCL2L1*).

The list of upregulated and downregulated genes can be used for the diagnosis of IBD and their types in Kurdish population. However, the co-expression reports of downregulated and upregulated genes and their interactions were used to identify candidate genes associated to the onset of IBD regarding their pathways (supplementary file Figure 1-6), for this purpose, shared upregulated genes (*RIT2, BCL2L1, MDM2,* and *FKBP8*) and downregulated genes (*NFKBIB, DDX24,* and *RASA3*) in UC and CD were used for further analysis through (KEGG database).

We found that *BCL2L1* and *MDM2* have roles in the following pathways (p53 signaling pathway and *NF-κB* signaling pathway) while the biological roles of *RIT2* and *FKBP8* not found on the *KEGG* database. Thus, their biological functions determined depending on the previous studies. we found that *NFKBIB* related to the (cytosolic DNA-sensing pathway, adipocytokine signaling pathway, B cell receptor signaling pathway, and chemokine signaling pathway), and *RASA3* related to the (Ras signaling pathway). While the pathway related gene for *DDX24* determined based on previous studies. Previous study evaluated the expression of mucosal genes in ulcerative colitis patients which reported the downregulation of NFKBIB in infected tissues. [16] Regarding the results of previous published study, *DDX24* negatively regulates cytosolic RNA-Mediated innate immune signaling. [17] Another study reveals that *DDX24* as an important regulator of p300 and suggest that the modulation of the p53-p300 interplay by *DDX24* is critical in controlling p53 activities in human cancer cells. [18] *RASA3* gene previously has not been associated with IBD, until, studies determined that differential methylation of *RASA3* could potentially alter endothelial–leukocyte adhesions, known to be of major importance for gut homing of inflammatory cells in IBD, targeted by drugs such as vedolizumab. [19]

Previous study measured *BCL2L1* expression levels in 116 paired CRC and normal tissues and CRC cell lines by qRT-PCR, they found that *BCL2L1* expression levels were significantly upregulated in the CRC tumor tissues and cell lines compared with the adjacent nontumor tissues. [20] Another experimental study on mice confirmed that the upregulation of *BCL2L1* related to the onset of IBD. [21] *MDM2* is a phospho-protein and a ubiquitin ligase for p53 that is responsible for inhibiting p53 activity and promoting its destruction. [22] Mutations in the *P53* gene have been identified in most human chronic diseases , as well as in its downstream signaling pathways, which are mediated by the *MDM2* genes; therefore, proper functioning of both genes is important for the normal function of cells. [23] Consequently, when mutations in any of these genes disrupt critical signaling pathways, they can result in chronic diseases including cancer. [24] and [25]

The variations in *RIT2* gene has been shown to be associated with a number of neurological disorders, such as Parkinson's disease (PD) and autism. [26] and [27] However, the immune signaling study in 2019 revealed that non-immune genes such as RIT2 can impact immune function

through the alteration of their expression. [28] *FKBP8* protein is located on the outer membrane and has an anti-apoptotic role by interacting with *Bcl-2*. [29] and [30] A study concluded that *FKBP8* plays an essential role in mitochondrial fragmentation through LIRL during mitophagy and this activity of *FKBP8* together with LIR is required for mitophagy under stress conditions. [31] Consequently, disruption of mitochondrial function and increased expression of genes or proteins indicative of mitochondrial fragmentation have been observed in neurological diseases, and in models of diabetes, intestinal inflammation, infection, and sepsis. [32]

Conclusions

In conclusion, our study has identified a list of genes exhibiting both upregulation and downregulation, which can serve as valuable tools for the diagnosis of inflammatory bowel disease (IBD). Additionally, the associated pathways related to these gene alterations represent promising targets for potential treatments.

It is essential to note that while our findings provide valuable insights into the genomic landscape of IBD, this study has its limitations, such as the relatively small sample size and the preliminary nature of the investigation. Therefore, caution should be exercised when interpreting and applying these results. Further research with larger and more diverse cohorts is warranted to corroborate our findings and enhance our understanding of the molecular mechanisms underpinning IBD.

Conflicts of Interest

The authors declare no conflict of interests.

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No funding was received for this study.

Author Contributions

BIM was primarily responsible for sample collection, laboratory investigation, and the biological analysis of the data. He played a critical role in gathering patient samples and conducting the necessary laboratory experiments. Additionally, he was actively involved in the analysis of

biological data. BKA contributed to the project by working on the research's template and conducting the statistical analysis. Her statistical expertise was instrumental in interpreting the research findings accurately. She also provided guidance and supervision throughout the research process, collaborating closely with the first author. Both authors collaborated in the preparation and writing of this research paper. The division of work between them was complementary, ensuring the successful completion of the study. All authors approved the final version of the manuscript.

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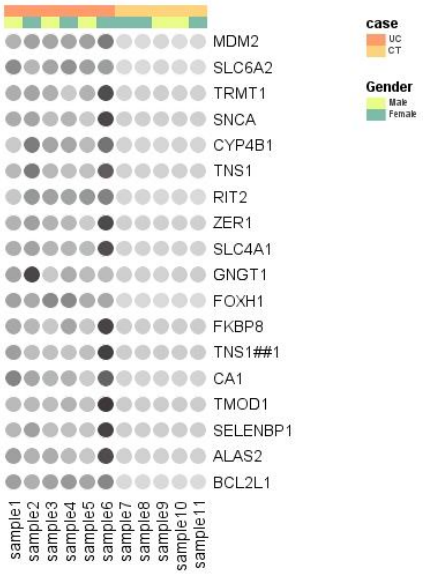

Figure 1: List of Upregulated genes in UC by Heatmap.

Dark color: highly expression.

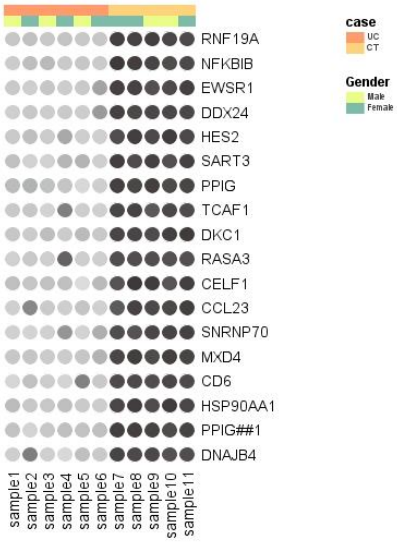

Figure 2: List of downregulated genes in UC by Heatmap.

Light color: low expression.

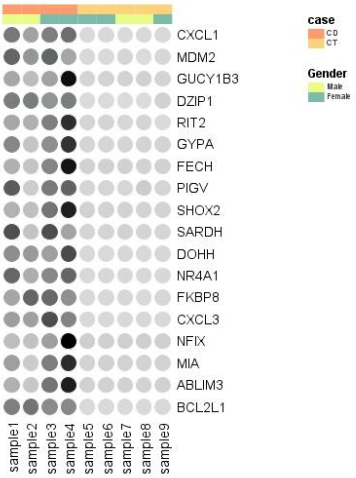

Figure 3: List of Upregulated genes in CD by Heatmap.

Dark color: highly expression.

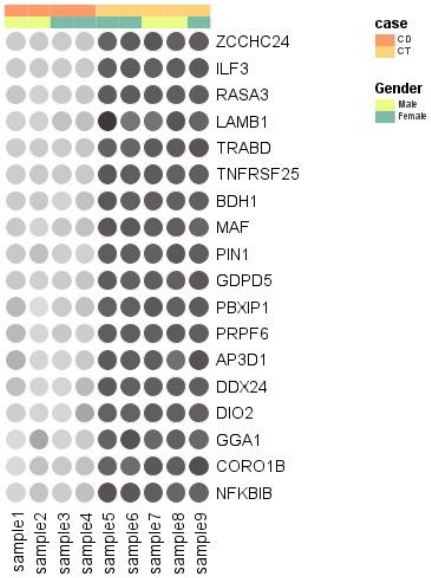

Figure 4: List of downregulated genes in CD by Heatmap.

Light color: low expression.