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Shared gene functions in autoimmune diseases identified via integrated bioinformatics analysis

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Abstract

Genetic transmission has minimal impact on autoimmune diseases compared to environmental factors. In conclusion, studies now focus on gene expression changes for diagnosis and treatment. This study used stringent cut-off values ($p < 0.05$, Log2(FoldChange) > 5) to monitor gene expression changes. Gene Ontology and Reactome Pathways enrichment analyses were performed, and interactions between differentially expressed genes (DEGs) were analyzed using the STRING database. Biomarker candidate genes were investigated across ten autoimmune diseases. Non-coding genes, particularly LINC01833 (upregulated in four diseases) and CD177 (upregulated in three diseases), were significant. The VCX, SLC, and KLK families were notably upregulated. Non-coding RNAs RNU5D-1 and MIR3648-1 were shared in two disease groups. Among shared genes between multiple sclerosis (MS) and ankylosing spondylitis (AS), ALPL, CHI3L1, HBM, MYL4, and PI3 were prominently downregulated. This study highlights the identification of differentially expressed signature genes across ten autoimmune diseases with high significance cut-offs ($p < 0.05$, Log2(FoldChange) > 5), suggesting their potential as significant targets for diagnosis and treatment.

Keywords: Autoimmune disease, Diagnosis, Treatment, Differentially Expressed Genes (DEGs), Non-coding RNAs.

1. Introduction

Autoimmune diseases can be defined as an abnormal condition that occurs when people's own immune cells do not recognize their own cells and attack them. It is seen that both genetic (genetically susceptible individuals) and environmental factors (environmental triggering) play a crucial role in the formation of these diseases. Autoimmune diseases, which consist of chronic and inflammatory diseases, cause serious pathological symptoms and significantly reduce the quality of life of the patient [1]. Although which organs affected depend on the type of autoimmune disease, more than one disease can often be seen in the same individual [2]. Generally, direct and indirect treatments for these multi-factorial and multi-symptom diseases are costly in the healthcare system [3]. Miller's claims in a 20023 review show that there are concerns that autoimmunity and autoimmune diseases are on the rise [4]. Therefore, researching the characteristics of these diseases and the data obtained can be used to suppress or treat the inflammatory features of the autoimmune diseases immediately.

The basis of autoimmune disorders lies in the interaction between genetic predisposition and environmental factors and how they are regulated. There are increasing findings that the effect of genetic transmission in diseases is responsible for approximately 25-40%, while the effect of environmental factors accounts for the remaining percentage [5]. Environmental factors may affect the occurrence of the disease in the organism or the severity of symptoms by affecting epigenetic changes and/or post-translational regulations. However, detecting the effects of environmental factors on the organism and examining them in detail involves very difficult and complex processes [6]. For this reason, ongoing studies still focus on genetic effects. Autoantibodies are biomarkers used in the diagnosis and classification of autoimmune disorders. However, it is not possible to diagnose with autoantibodies, especially if symptoms develop against autoantigens synthesized as intracellular molecules [6]. Therefore, new biomarkers are needed for the diagnosis and treatment of autoimmune diseases.

With the widespread use of RNA-seq analyses, it is possible to compare samples taken from healthy and sick people and thus to discover markers related to relevant diseases [7]. RNA-seq data, which has accumulated rapidly in recent years, will enable the discovery of biomarkers of diseases and potential drugs for these markers. A large amount of data from 10 different autoimmune diseases

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(including ankylosing spondylitis (AS), Crohn's disease (Crohn's), juvenile idiopathic arthritis (JIA), polymyositis and dermatomyositis (PD), psoriasis (PS), multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), muscular dystrophy (MD) and ulcerative colitis (UC)) was combined with a transcriptome atlas made by the Shen group in 2022 [8]. By using the bulk RNA-seq analysis section on this platform, it has become easier to analyse the gene differences between the mentioned diseases and understand the correlation relationship between them. These conditions vary in their specific manifestations, affected organs, and treatment approaches, but they share common underlying mechanisms involving genetic predisposition and environmental triggers. AS is a chronic inflammatory arthritis primarily affecting the spine and sacroiliac joints, leading to pain and stiffness. It affects about 0.5% of the adult population of European descent and typically begins in adolescence or early adulthood [9]. Crohn's and UC are types of inflammatory bowel diseases (IBD) characterized by chronic inflammation of the gastrointestinal tract. They can cause abdominal pain, diarrhea, and weight loss [10]. JIA is the most common form of arthritis in children, causing persistent joint inflammation [11]. PD are inflammatory myopathies that cause muscle weakness and skin rashes, respectively [11]. PS is a skin condition that causes red, scaly patches [12]. MS involves the immune-mediated destruction of myelin in the central nervous system, leading to neurological symptoms [13]. RA is a systemic inflammatory disorder affecting joints, leading to pain and deformity [10]. SLE is a systemic autoimmune disease affecting multiple organs, characterized by periods of flare-ups and remission [10]. MD is a group of genetic disorders causing muscle weakness and degeneration [14].

In this study, I particularly focused on translated genes. The changes in the amount of genes identified as upregulated and downregulated in different autoimmune diseases were examined, and pathway analyses of those with commonalities were performed. Nevertheless, it is crucial not to disregard the shared characteristics of long non-coding RNAs, particularly those exhibiting variations in expression across multiple autoimmune diseases.

2. Materials and methods

2.1. Patient sizes and general design of research

The schematic overview of our study is shown in Figure 1. The numbers of individuals used in this study, in which 10 different autoimmune diseases were compared using the IAAA platform [15], are as follows: healthy (64)(not shown on figure), SLE (488), MS (34), Crohn's (142), AS (44), JIA (108), UC (14), RA (12), PS (9), MD (7) and PD (7). In order to identify the most influential genes in autoimmunity, highly stringent cut-off values were utilized. Therefore, the p-value cut-off was 0.05 and Log2(FoldChange) cut-off was 5.

2.2. Enrichment and pathway analyses of shared genes

Differentially expressed genes (DEGs) and/or hub genes obtained from IAAA data were subjected to Gene Ontology (GO) enrichment analysis using the Annotation, Visualization and Integrated Discovery (DAVID, v2023q4) database [16]. A significant p-value of <0.05 was considered significant. Gene Ontology (GO) enrichment analysis was performed to help identify high-throughput molecular function, biological process and cellular components in biological data [17]. The data utilization for this objective was acquired through the comparison of up-regulated genes, focusing on the selection of genes shared between Crohn's disease and ankylosing spondylitis (AS), as these groups exhibit the greatest overlap in common genes. The study of gene ontology (GO) data, focusing on downregulated genes, was conducted comparing ankylosing spondylitis (AS) and multiple sclerosis (MS), revealing the highest degree of shared genes between these conditions. Pathway analyses of the relevant genes were performed using the Reactome Pathway Database (https://reactome.org) web-tool [18].

To better understand the potential biological relevance of changes in up-regulated or down-regulated gene expression commonly observed in autoimmune diseases, annotated genes with varying levels were uploaded to the Panther Gene Ontology Classification System (v14) [19]. The uploaded data were then mapped to genes within the PANTHER classification system. Statistical overrepresentation testing was used with the Panther GO-slim Biological Process and the Panther GO-slim cellular component to identify the potential biological impact of changes in gene levels.

2.3. Protein-protein interaction (PPI) network analysis

Gene information in PPI networks was downloaded from the STRING database (https://string-db.org/). All PPI networks were run in Cytoscape v3.7.2 (https://cytoscape.org/) [20] for network analysis of genes shared between different diseases according to their level of regulation.

3. Results

3.1. Differentially expressed and shared genes of autoimmune diseases

Differentially expressed genes belonging to 10 different autoimmune diseases registered on the IAAA platform were compared and the results are shown in Figure 2. In the selection of differentially expressed genes, log2(FC) value of 5 and p value <0.05 were taken into consideration. Figure 2A shows the commonalities of genes that are upregulated, while Figure 2B shows the intersections of gene partnerships that are downregulated. When looking at the upregulated genes, there is a distinction into 2 main groups, as a result of which UC, PD and MD appear as a group, Crohn's, AS, SLE and RA appear as a digger group (Groups that are not displayed do not exhibit an increase in

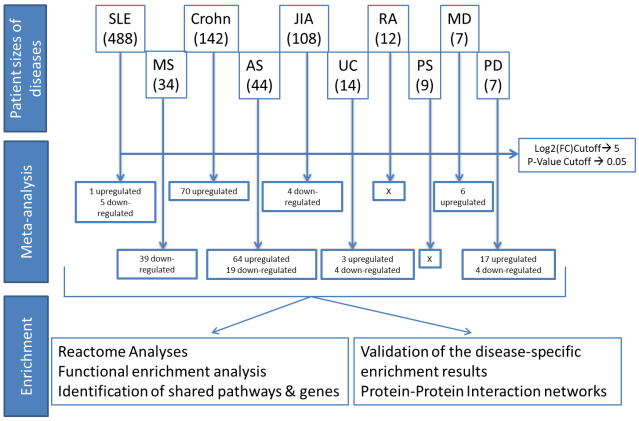

Fig. 1. The schematic overview of the study.

shared upregulated genes according to these threshold values.). When examining the first group, it is observed that CD177 gene is shared commonly among three members, while between PD and MD, the sharing of three genes (AHSP, CA1, ALAS2) is noted. On the other hand, upon analysing the second group, it is evident that the largest intersection set consisting of 64 genes is found between Crohn's disease and Ankylosing Spondylitis (AS)(Supplement Table 1). Additionally, it is observed that the LINCO1833 gene responsible for long non-coding RNA synthesis is commonly shared among four different diseases (Crohn's, AS, Systemic Lupus Erythematosus (SLE), and Rheumatoid Arthritis (RA)).

When the differentially expressed downregulated genes were compared, it was observed that 6 different diseases had shared genes by exceeding the determined threshold values (Figure 2B). These 6 different diseases are also divided into 3 different subgroups. It was found that the members of the first group were JIA and SLE, the members of the second group were UC and PD, and the members of the third and largest group were MS and AS. The members of the first group and the second group each have one shared gene. These are RNU5D-1 and MIR3648-1, respectively. The downregulated genes shared by the members of the third group were found to be ALPL, CHI3L1, HBM, MYL4 and PI3.

3.2. Gene ontology analysis results of shared genes

Gene Ontology analysis was performed to elucidate the underlying mechanisms contributing to disease pathogenesis by identifying enriched GO terms associated with genes differentially expressed as shared upregulated or downregulated when comparing diseases. According to the results obtained, Figure 3A shows the results of shared and upregulated genes in AS and Crohn's diseases in terms of GO terms. It was found that catalytic activity, signaling receptor activity and binding activities (signaling receptor binding, metal ion binding, small molecule binding) were the most hit functional units in molecular function analysis. According to the biological process results, it was observed that response to stimulus and signaling processes were the most hit areas. Cell differentiation and developmental processes follow them. Cellular component results also show that the area where the most function occurs is the plasma membrane, followed by the nucleus.

Figure 3B illustrates the Gene Ontology (GO) results of genes shared between MS disease and AS, which are downregulated. Upon individual examination of each of the three GO terms, it is observed that within the molecular function category, the majority of activity occurs within the catalytic activity group. In terms of biological processes, developmental processes and responses to stimuli exhibit higher activity compared to others. Within the cellular component category, activities related to the extracellular region and plasma membrane are notably high.

3.3. Pathway analyses of shared genes panther analysis of shared & upregulated genes

The results of Panther pathway analysis have been examined in three separate categories (Figure 4 (A-C)). According to these results, in the biological process category, the ones with the highest share are, in descending order, cellular process, biological regulation, multicellular organismal process, response to stimulus, and homeostatic process. In the Cellular Component category, only two groups have been found, which are protein-containing complexes and cellular anatomical entities. In the third and final category, molecular function, the group with the highest share is binding. Following this group, in descending order, are molecular transducer activity and molecular function regulator activity, which are the other major groups.

When pathway analysis was conducted using the Reactome platform for upregulated and shared genes, the results are presented in the Supplement Table 2 was obtained. As shown in the table, six paths are listed at the $p < 0.05$ criterion. The top two groups sharing the first two ranks are the expression and translocation of olfactory receptors and olfactory signaling pathway, both affecting olfactory activities. Interleukin-20 family signaling is also among the pathways with high hits. RHO GTPases regulate CFTR trafficking, Sensory Perception, and Interaction

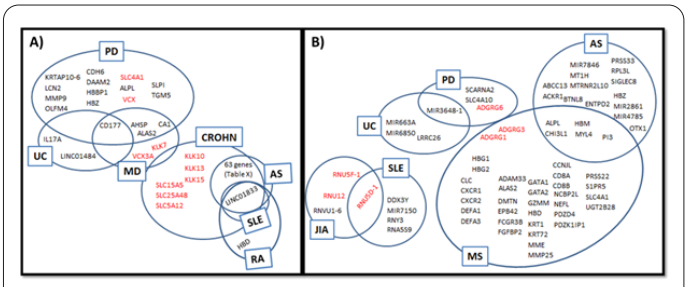

Fig. 2. Shared genes based on their expression level differences in autoimmune diseases. A) Upregulation-based comparison. B) Downregulation-based comparison.

Fig. 3. Gene Ontology Analysis of (A) Upregulated Genes Shared in both Crohn's and AS diseases, (B) Downregulated Genes Shared in both MS and AS diseases.

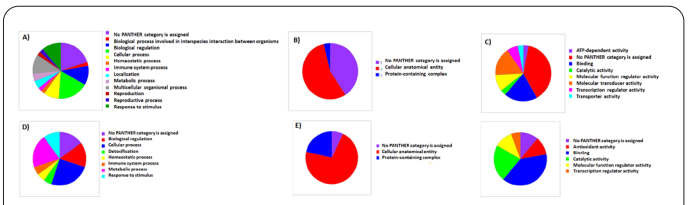

Fig. 4. Panther analysis result of upregulated and shared genes between AS & Crohn's. A) Biological Process B) Cellular Component C) Molecular Function. Panther analysis result of downregulated and shared genes between AS & MS. D) Biological Process E) Cellular Component F) Molecular Function Results

With Cumulus Cells And The Zona Pellucida are listed as other pathways within this group. (Although it has been demonstrated that four genes are shared between PD and MD, statistically significant results could not be achieved when they were included in Panther and Reactome analyses. Therefore, the results of these analyses are not presented.)

For a more comprehensive exploration of protein-protein relationships, interaction analyses were conducted using Cytoscape for shared genes between different groups. According to Figure 5A, as observed, genes shared between PD and MD demonstrate high interactions with each other directly and/or indirectly. Additionally, they are observed to interact with 20 other proteins apart from themselves. Figure 5B illustrates the interaction map of shared genes between AS and Crohn's disease. The results indicate that the shared genes interact in four different groups. In the first and largest group, consisting of 15 shared genes, it is observed that they interact with 14 different proteins as well. FLG2 and CFTR proteins interact solely with themselves among these proteins, while CABCOCCO1 interacts with two, and ATP4B interacts with four different proteins.

When downregulated genes between AS and MS are listed under three categories in Panther analysis (Figure 4 (D-F)), the results show that in the first category, biological processes, cellular process has the highest share. Following it, metabolic process, biological regulation, and response to stimulus groups are also listed. Looking at the results for cellular components, similar to the upregulated group, only two groups are found, which are cellular anatomical entity and protein-containing complex. In the molecular function category, five groups are listed, with binding and catalytic activity observed to have the highest shares, respectively.

For pathway analysis using the Reactome platform, statistically significant downregulated genes are listed in six groups. Among these listed groups in the Supplement. Table 3, two pathways associated with metal are found: Metallothioneins bind metals and Response to metal ions pathways.

When protein-protein interaction analysis was conducted using Cytoscape for the downregulated shared genes, it was observed that these 5 genes were associated with 20 different proteins. Particularly, protein exhibited high interaction with 4 proteins (MYBPC3, MYH6, TNNI2, TNNT2), while HBM showed high interaction with 5 proteins (HBA1, HBA2, HBB, HBD, HBQ1)(Figure 5C).

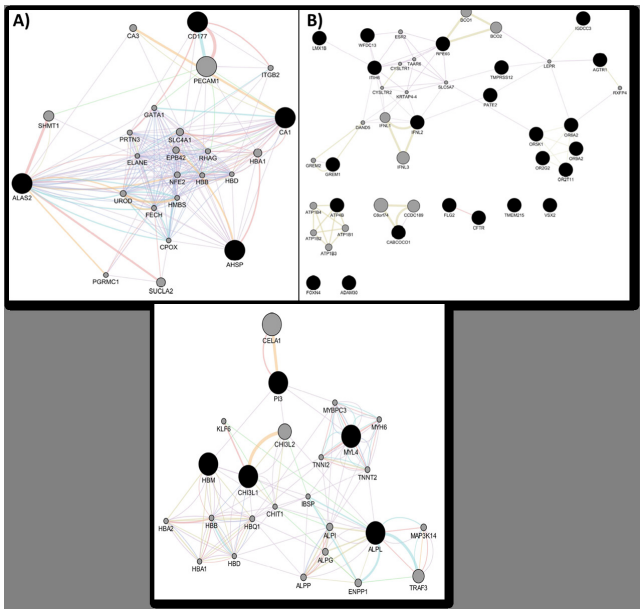

Fig. 5. Protein-protein interaction of upregulated (A) PD and MD, (B) AS and Crohn's shared genes and their interacted proteins (C) Protein-protein interaction of downregulated AS and MS shared genes and their interacted proteins (Black ones are shared genes, Gray ones are their interacted proteins) .

4. Discussion

Research on genes associated with autoimmune diseases with increased expression has shown that non-coding RNAs, as well as CD177, VCX family, SLC and KLK family and CHI3L1 genes, play an active role. CD177, a glycoprotein found on the surface of neutrophils, plays significant roles in neutrophil function. Although it has been associated with some diseases, such as cancer, it has not yet been linked to autoimmune diseases. It has been suggested that it appears in these diseases due to the immune system's overactivity associated with inflammation, but its exact role in pathogenicity has not been studied. In this study, I worked with a fold change > 5. Despite this high score, the presence of this protein in three autoimmune diseases, PD, MD, and UC, indicates that its high expression in at least these three diseases was significant.

4.1. Common upregulated genes

When comparing the upregulated genes among autoimmune diseases, it has been observed that there are three shared genes in two diseases (AHSP, ALAS2, and CA1), one affecting the muscle system (MD) and the other affecting the neuron system (PD). Upon investigation, these genes are seen to play roles in oxygen transport and heme regulation. Thus, a significant commonality between PD and MD is an issue with oxygen transport mechanism-wise.

In addition to the three genes mentioned above, it is thought that the VCX (in PD) and VCX3A (in MD) genes, although not shared, are also upregulated in these diseases and warrant further investigation due to their high degree of sequence similarity. Both of these genes are located on the X-chromosome and belong to the VCX family. In particular, these two genes show high homology compared to other members of the family. According to Labonne et al (2020), VCX3A has been associated with cognitive impairments [21]. The findings of this study suggest that MD, in addition to PD, which is mentioned as neuronal inflammation, can also be associated with the VCX family.

The potential locations of different SLC (solute carrier) family genes in the cell and their roles in RA are well summarized by Torres et al. (2022) [22]. In this study, it was observed that PD and MD had separate genes that showed homology with Crohn's disease. Of these, SLC family proteins, SLC4A1, were found to be active in PD and SLC15A5, SLC25A48, and SLC5A12 were found to be active in Crohn's disease. SLC15A5 has been found to play a role in dysregulation of lysosomal function and protein degradation pathways, autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). In this study, it was shown that this gene is also highly expressed in Crohn's. It has been shown that this protein family, which is found very effectively in dis-

eased and healthy individuals, may be associated not only with SLE, RA and Crohn's, but also with other autoimmune diseases.

Increases in the expression of 4 genes belonging to the KLK family (KLK7 in MD; KLK10,13 and 15 in Crohn's) have been observed in MD and Crohn's diseases. Previous studies of the KLK family have revealed their high interaction with skin inflammation in another autoimmune disease, such as atopic dermatitis [23]. Another study revealed the importance of KLK family members for epidermal homeostasis [24]. Their active presence in this study shows that in autoimmune diseases, especially Crohn's and MD, the extracellular region and skin barrier are exposed to high levels of inflammation and cell repair is attempted there.

4.2. Common downregulated genes

When looking at downregulated shared genes, non-coding RNAs stand out at first glance. The first one I will cover is RNU5D-1, which is shared between JIA and SLE. It is known that RNU5D-1 is involved in spliceosomal tri-snRNP complex assembly. MIR3648-1, shared between PD and UC, appears as another non-coding RNA type that is downregulated. Previous studies have revealed that SOCS2 activity is inhibited by the activation of this gene. The reason why it was highly downregulated in this study is that it is due to high cytokine activity in autoimmune diseases.

It has been shown that 5 different genes (ALPL, CHI3L1, HBM, MYL4 and PI3) are shared downregulated between MS and AS. CHI3L1 is a protein secreted from different cell types, from macrophages to muscle cells, and whose biological function has not yet been fully determined, but it has been associated with autoimmune diseases. A comprehensive review study conducted in 2022 examined the relationship of the CHI3L1 gene with different autoimmune diseases [25]. According to this study, the most significant result was found between RA and high-level CHI3L1, and it was revealed that it can be used as a biomarker for this disease and even the injection of this protein can be used in treatment as an immunomodulator. The low-level expression of this protein in RA patients has shown that it can be used as a marker showing the effectiveness of applied therapies [25]. Various studies have shown that CHI3L1, which is expressed at a similarly high level in MS patients, is associated with progressive or relapsing MS [26,27]. This study revealed that this protein is downregulated in AS and MS diseases, contrary to the generally upregulated CHI3L1 studies. In another study, except for relapses, CHI3L1 levels remained high only in patients with progressive MS [26]. Considering these situations, the conclusion that can be drawn is this: The progression of MS disease can be detected by looking at CHI3L1 levels. It appears that the groups included in this study are not progressive MS or relapsed MS. Studies on AS reveal that heart problems are affected if the expression of this protein is high [28]. This study showed that changes in the expression status of this gene for both MS and AS can provide information about the course of the disease.

One of the genes found to be downregulated is the ALPL gene. It has been shown by various groups that the dysfunction of this gene, which expresses an alkaline phosphatase, is closely related to the systemic effects it causes in digestive and autoimmune diseases [29] and systemic inflammation [30]. The possibility of ALPL being an important biomarker in autoimmune diseases has been previously emphasized [31]. As a result of this study, the ALPL gene was found to be downregulated, revealing that the decrease in this gene expression may be associated with autoimmune diseases, especially MS and AS.

Peptidase inhibitor 3 (PI3), known for its antimicrobial and anti-inflammatory roles [32], was found to be highly expressed in individuals with psoriasis compared to healthy individuals [33]. Psoriasis is known as an inflammatory skin disease, an immune disorder, and in the study by Deng et al., the high expression of the PI3 gene has been suggested as a potential biomarker for this disease [33]. In a subsequent study the following year, it was suggested that high-expression PI3 could be associated with the prognosis of celiac disease [34]. Despite studies suggesting otherwise, this research indicates that significant decrease in the expression of this gene in the cases of MS and AS diseases may also indicate the presence of different biomarkers and therapeutic targets in autoimmune diseases.

The association of HBM with autoimmune diseases has been explained as an increase in gene expression in response to oxidative stress [35]. However, the down-regulation observed in this study in MS and AS diseases creates a contradiction regarding this gene. Therefore, further studies are needed to associate HBM with autoimmune diseases.

The correlation between MYL4, especially those associated with muscle-related autoimmune diseases, has been highlighted in studies of other groups [36,37]. It is known that this gene, highly expressed during the embryonic period, decreases in expression as development progresses. However, it has been found to be highly expressed in Immune-mediated necrotizing myopathy (IMNM), a muscle-related autoimmune disease [36]. This has been interpreted as an effort by the organism to repair muscle damage. Furthermore, the high expression of MYL4 has been validated as an autoantibody for myositis, demonstrating its potential utility in screening and diagnosis [37]. Similar to HBM, this study on MYL4 also yields contradictory results compared to the literature. While there is reported increase in expression in autoimmune muscle diseases in the literature, in this study, gene expression is significantly decreased in MS and AS diseases. Therefore, despite requiring further investigation, it can be said that there is a specific condition for MS and AS regarding MYL4.

4.3. Long and short non-coding RNAs

Long non-coding RNAs (lncRNAs) in autoimmune diseases have been an active area of research [38]. Non-coding RNAs (ncRNAs) are functional transcripts and most are not translation-related. In the study of Cheng et al. (2023)[39], ncRNAs and their presence in different autoimmune diseases were examined. This study also shows that the relationship of non-coding RNAs with autoimmune diseases is one of the issues that needs to be focused on. Within the scope of this study, their occurrence even in case of fold change>5 supports this result. Interestingly, in this study, a single gene was found to be shared by Crohn's, AS, SLE and RA, which is LINC01833, a long non-coding RNA. However, despite this high score, its significant presence in all 4 diseases shows that it deserves

attention. While a direct connection between LINC01833 and autoimmune diseases has not yet been established, investigation into this non-coding RNA and its targets has revealed miR-519e-3p. Although studies on the association of LINC01833 with lung adenocarcinoma and cervical cancer have gained momentum in recent years [40-42], its role in autoimmunity remains largely unexplored. A study conducted in 2020 demonstrated a direct interaction between LINC01833 and this microRNA [43]. It has been shown that miR-519e-3p plays an inhibitory role on S100A4. S100A4 protein has been discussed in many studies as a potential biomarker or therapeutic target in immune-mediated diseases [44]. In this study, the high presence of LINC01833 and the inhibition of miR-519e-3p are thought to lead to an increase in S100A4 in these diseases, affecting disease prognosis. Thus, LINC01833 is suggested to be a strong therapeutic target for autoimmune diseases.

4.4. Functional relationships between gene families

When the pathway results expressed as both downregulated and upregulated were compared, it was observed that the changes in the biological regulation, cellular process, homeostatic process, immune system process, metabolic process and response to stimulus groups, which are related to biological processes, occurred in common. Unlike each other, localization and reproductive categories were found to be effective in the upregulated group, while detoxification was found to be effective in the downregulated group. Higher transduction (signaling) activity was observed in genes that were upregulated compared to those that were downregulated in molecular function.

According to Reactome results, upregulated gene expressions actively activate the sensory signaling pathway and interleukin signaling pathways. It was observed that downregulated genes mostly activate the response to metal &/or metalloid ions pathways. Therefore, in autoimmune diseases, there is more of a systemic response rather than a stress response.

Autoimmune diseases arise from a complex interplay between genetic susceptibility and environmental triggers such as infections, dietary factors, and toxin exposure—factors that are increasingly prevalent in modern life. In this context, every effort to better understand the molecular underpinnings of autoimmunity is of growing importance.

This study highlights that both coding and non-coding RNAs contribute significantly to the pathogenesis of autoimmune diseases. Notably, genes such as CD177 and the long non-coding RNA LINC01833 were highly expressed in multiple disease contexts, suggesting their involvement in immune activation. Conversely, downregulated genes like CHI3L1 and ALPL may reflect disease progression stages or immune regulatory mechanisms.

These findings support the presence of shared molecular mechanisms across distinct autoimmune conditions, despite their clinical differences. The identification of common and unique gene expression signatures not only provides insight into disease biology but also opens the door for the development of novel diagnostic biomarkers and therapeutic targets. Further validation in patient-derived samples and functional studies on highlighted gene candidates is warranted to translate these molecular insights into clinical applications.

Statements & declarations

Conflict of interest

The authors declare that they have no competing interests.

Ethical statement

Not applicable.

Consent for publıcatıon

Not applicable.

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This study did not receive any funding from a particular source.

Data availability statement

The manuscript contains all data supporting the reported results. The raw data used in this study are available online (https://galaxy.ustc.edu.cn/IAAA). Additional questions can be directed to the relevant author(s).

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