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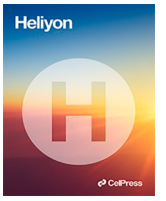

Research article

Elucidating genetic intersections: Co-differentially expressed genes in myasthenia gravis and idiopathic inflammatory myopathies and their role in comorbid pathogenesis

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ABSTRACT

Background: Myasthenia gravis (MG) and idiopathic inflammatory myopathies (IIM) are autoimmune disorders that can co-occur, complicating diagnosis and treatment. The molecular mechanisms underlying this comorbidity are not well understood.
Objective: This study aims to identify common differentially expressed genes (co-DEGs) between MG and IIM to elucidate shared pathogenic pathways and potential therapeutic targets.
Methods: Transcriptomic data from the Gene Expression Omnibus (GEO) were analyzed using the "limma" package in RStudio. Functional enrichment analyses were performed using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. A nomogram prediction model was developed, and receiver operating characteristic (ROC) analysis was used to evaluate its diagnostic potential.
Results: Four co-DEGs were identified between MG and IIM, associated with neurotransmitter transport and ion channel regulation. The nomogram model, incorporating three of these co-DEGs, showed high predictive accuracy for MG with IIM complications, with an area under the ROC curve of 0.94. Immune infiltration analysis revealed distinct patterns in MG and IIM, particularly involving gamma delta T cells and activated mast cells.
Conclusion: The study identifies key genetic intersections between MG and IIM, providing insights into their shared pathogenesis and highlighting potential diagnostic and therapeutic targets. Further experimental validation is required to confirm these findings.

1. Introduction

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disorder that primarily affects the neuromuscular junction, resulting in muscle weakness and fatigue [1]. The clinical manifestations of MG are highly variable, with symptoms often being more pronounced in the ocular and bulbar muscles, leading to difficulties in vision, speech, and swallowing [2]. The etiology of MG involves the production of autoantibodies against components of the neuromuscular junction, such as the acetylcholine receptor (AChR), which impair neuromuscular transmission [2].

Idiopathic inflammatory myopathies (IIM), on the other hand, are a group of rare, heterogeneous autoimmune disorders

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characterized by muscle inflammation and weakness [3]. The principal subtypes of IIM include polymyositis (PM) and dermatomyositis (DM), each with distinct clinical and pathological features. While MG and IIM are distinct entities, there are cases where these two conditions coexist, complicating both diagnosis and treatment [4]. The simultaneous occurrence of MG and IIM, though rare, represents a significant clinical challenge due to the overlapping and potentially synergistic pathogenic mechanisms.

Recent studies have suggested that autoantibodies against intracellular targets, such as the ryanodine receptor and titin, may play a role in the pathophysiology of MG, particularly when complicated by myositis [5,6]. These antibodies have been associated with more severe forms of MG and the presence of myopathy. However, the precise mechanisms by which these autoantibodies contribute to disease pathogenesis remain poorly understood [7–9].

Given the complexity and clinical significance of MG and IIM comorbidity, it is crucial to elucidate the molecular mechanisms underlying this relationship. This study aims to bridge this knowledge gap by leveraging transcriptomic data to identify common differentially expressed genes (co-DEGs) in MG and IIM. By analyzing these co-DEGs, we seek to uncover shared molecular pathways that may contribute to the comorbidity of these diseases. Additionally, we aim to explore potential therapeutic targets that could lead to more effective treatments for patients suffering from both MG and IIM.

In this context, we utilized publicly available datasets from the Gene Expression Omnibus (GEO) database to conduct a comprehensive comparative analysis. The findings of this study not only enhance our understanding of the genetic intersections between MG and IIM but also provide insights that could inform the development of targeted therapies for these complex autoimmune conditions.

2. Methods

2.1. Data acquisition

This study involved the analysis of two distinct datasets from GEO database. The first dataset, designated as the MG dataset (GSE accession ID: GSE85452), comprised blood samples from 13 patients diagnosed with MG and 12 healthy controls, including 3 monozygotic twins of the MG patients. The remaining 9 healthy controls were incorporated into further analyses. The IIM dataset, divided into three subsets (GSE accession IDs: GSE5370, GSE128470, and GSE3112), contained muscle tissue samples from patients with various forms of IIM, including DM, PM, and inclusion body myositis (IBM), along with samples from healthy controls. Certain subsets of patients, notably those with IBM and nonspecific myopathies (NS), were excluded to streamline the focus on specific IIM conditions.

2.2. Identification of co-DEGs

Differential expression analysis was performed using the limma package in RStudio (version 4.21). Criteria for identifying differentially expressed genes (DEGs) were set at $|\text{Log2 Fold Change}| > .58$ and $|\text{adjusted P-Value}| < .05$. Results were visualized using volcano plots and heatmaps to highlight significantly expressed molecules. The ggplot2 package facilitated the creation of Venn diagrams for identifying and visualizing common DEGs between MG and IIM datasets. Subsequent Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were conducted using the clusterProfiler package in RStudio (version 4.1.2), applying a p-value threshold of < 0.05 for significance.

2.3. Analysis of immune infiltration

Immune cell infiltration was analyzed using the CIBERSORT algorithm via the CIBERSORTx website and the ssGSEA algorithm, based on 24 immune cell markers from a 2013 Immunity article [10]. The Mann-Whitney *U* test compared immune cell infiltration differences between diseased and healthy groups, identifying statistically significant immune cells. Common differentially infiltrating immune cells in MG and IIM were then selected for further analysis.

2.4. Analysis of PPI network based on co-DEGs

Protein-protein interaction (PPI) network analysis was performed using the STRING website (https://string-db.org/), employing a combined score threshold of 0.9. This analysis provided insights into the cellular and molecular interactions underlying MG and IIM.

2.5. ROC analysis and model evaluation

Receiver Operating Characteristic (ROC) analysis was conducted for each common DEG in the MG and IIM datasets using the pROC and ggplot2 packages in RStudio. A Nomogram prediction model based on the co-DEGs was developed using the rms and ResourceSelection packages. The model's performance was evaluated through ROC analysis, calibration curves, and decision curve analysis (DCA).

2.6. Evaluation of applicant drugs

The Drug Signatures Database (DSigDB) was utilized to explore the molecular properties of drugs targeting MG and IIM [11]. This analysis, conducted through the Diseases/Drugs function in Enrichr, aimed to identify potential therapeutic agents by focusing on

drugs that modulate genes associated with these conditions.

2.7. Gene-disease association analysis

This analysis, conducted through the Diseases/Drugs function in Enrichr, aimed to identify potential therapeutic agents by focusing on drugs that modulate genes associated with these conditions [12–15]. Visualization of these networks was achieved using graphing tools in RStudio (version 4.1.2).

All the above analysis work and visualization are done using RStudio (version 4.1.2).

3. Results

3.1. Identification of DEGs and common DEGs between MG and IIM datasets

A flowchart (Fig. 1) delineates the key steps of our study. We analyzed blood and muscle samples from the GEO database to examine the interplay between MG and IIM. Post-normalization, box plots illustrating gene expression levels in the MG and IIM datasets are shown in. Following stringent cutoffs ($|\text{Log2 Fold Change}| > 0.58$, p-value <0.05 for MG; $|\text{Log2 Fold Change}| > 0.585$, $|\text{adj. P. Val.}| < 0.05$ for IIM), we identified 121 DEGs in MG and 1396 DEGs in IIM (Fig. 2A and B). Volcano plots further visualize these DEGs (Fig. 2C and D). A Venn diagram identified four common DEGs (SLC30A1, CLE2B, SIDT2, TAGLN) in both datasets (Fig. 2E), suggesting shared genetic pathways in MG and IIM, with implications for understanding disease pathogenesis and potential therapeutic targets.

3.2. Functional enrichment analysis of co-DEGs

Using the "ClusterProfiler" package, GO and KEGG enrichment analyses were conducted (Fig. 2F and G). GO analysis identified significant pathways related to signal release, neurotransmitter secretion and transport, calcium ion import, and detoxification of inorganic compounds. Molecular function analysis highlighted key GO terms with p-values <0.05. In KEGG analysis, pathways like Mineral Absorption and Kaposi Sarcoma-Associated Herpesvirus Infection were significant.

3.3. Analysis of immune infiltration

In the patient cohort with MG, our analysis revealed distinct patterns of immune cell infiltration compared to the healthy control group. Specifically, elevated levels of T cell CD4 naive, T cell gamma delta, and Mast cell infiltration were observed in MG patients. Conversely, the infiltration levels of activated Mast cells, Plasma cells, T follicular helper cells, and effector memory T cells (Tem) were comparatively lower in MG patients than in the healthy group.

In contrast, patients diagnosed with IIM exhibited a different immune profile. Notably, the infiltration levels of gamma delta T cells,

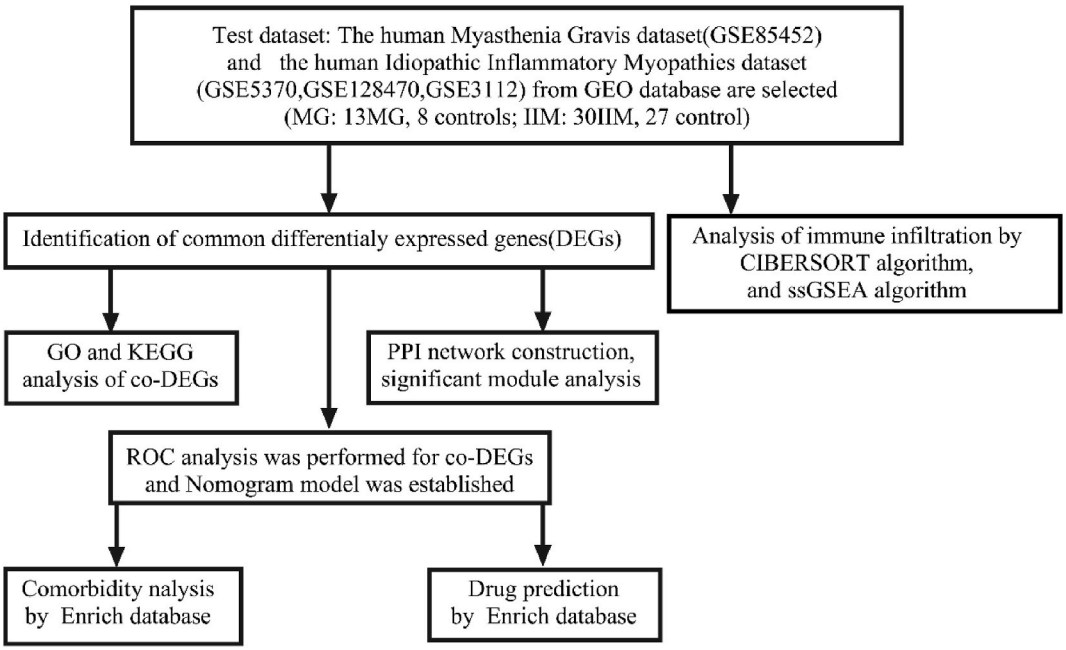


Fig. 1. Flow chart of Transcriptome analysis revealed the crosstalk between Myasthenia gravis and Idiopathic inflammatory myopathies.

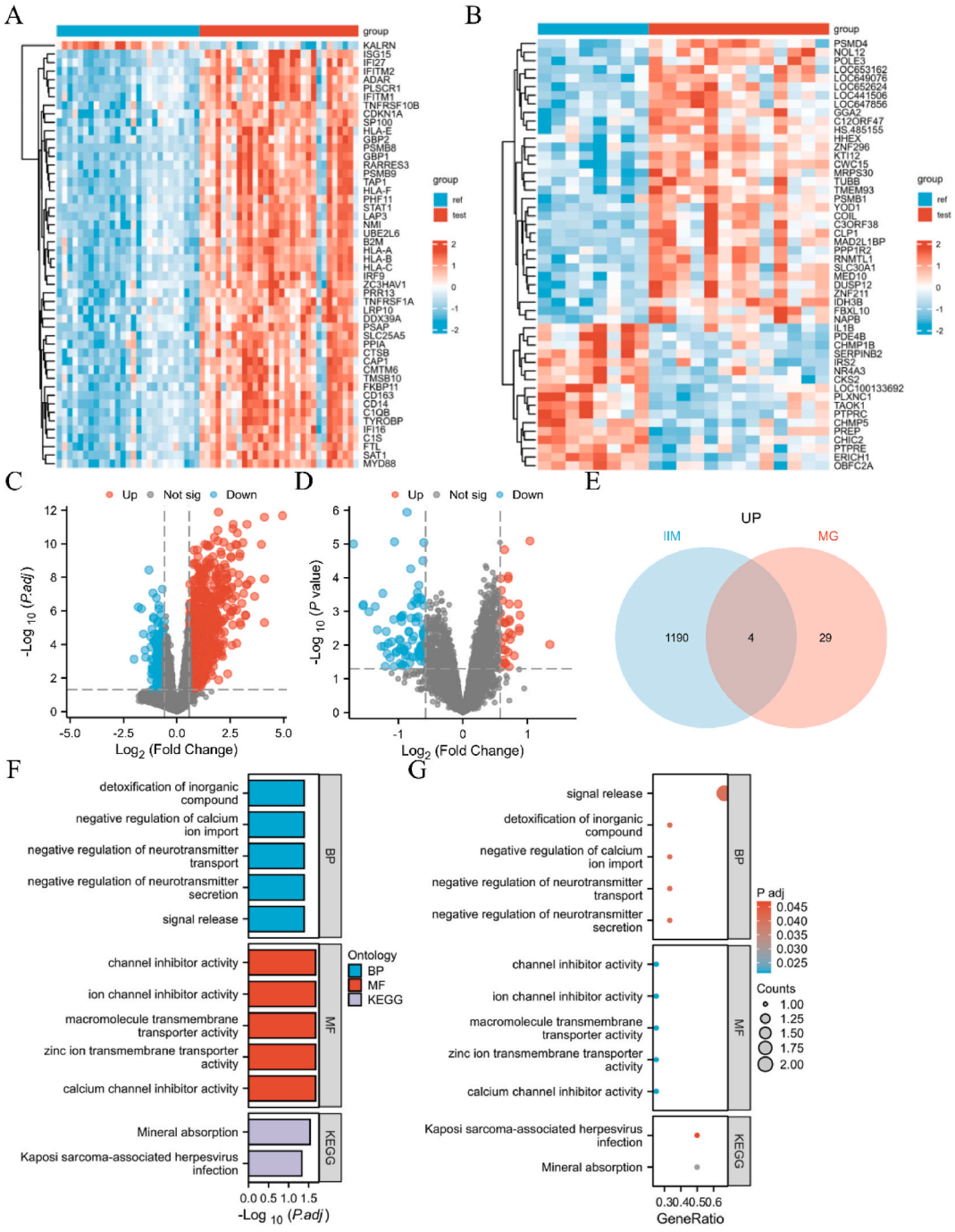


Fig. 2. A, C the expression heat map and volcano map of the IIM group; B, D the expression heat map and volcano map of the MG group; E Venn diagram of MG versus IIM DEGS; F, G Bar and bubble plots of co-DEGs for GO and KEGG analysis.

M1 and M2 Macrophages, activated dendritic cells (aDC), B cells, CD8 T cells, Cytotoxic cells, dendritic cells (DC), memory B cells, immature dendritic cells (iDC), plasmacytoid dendritic cells (pDC), and T follicular helper cells (TFH) were higher in IIM patients compared to the healthy controls. However, levels of T cell CD4 naive, regulatory T cells (Tregs), resting NK cells, activated Mast cells, Eosinophils, NK CD56dim cells, and T helper cells were found to be lower in IIM patients than in the control group.

Overall, both MG and IIM patient groups showed increased infiltration of gamma delta T cells, while the level of activated Mast cell infiltration was lower compared to the healthy group. These immunological findings shed light on the distinct and shared pathways of immune system involvement in MG and IIM, suggesting potential targets for therapeutic intervention.

3.4. PPI network

Utilizing the STRING database, we analyzed protein-protein interactions among shared DEGs between MG and IIM. An interaction between SIDT2 and TAGLN was noted, with a combined score of 0.321.

3.5. ROC analysis

In our evaluation of the prognostic capacity of the co-DEGs identified within the MG and IIM datasets, ROC analysis was employed. The analysis revealed AUC values ranging from 0.76 to 0.91 in the MG dataset and from 0.73 to 0.95 in the IIM dataset, as depicted in Fig. 3 (Fig. 3A–H). These significant AUC values underscore the notable predictive power of these co-DEGs, thereby accentuating their potential as key gene targets for novel therapeutic approaches in MG and IIM contexts.

To further enhance its diagnostic applicability, we developed a Nomogram prediction model, particularly aimed at diagnosing MG patients with IIM complications. In both MG and IIM datasets, multiple logistic regression analyses were conducted utilizing the four common co-DEGs to construct respective Nomogram models (Fig. 4A). The MG Nomogram model incorporated three of these genes, while the IIM model encompassed all four. Notably, the MG Nomogram model demonstrated greater suitability for diagnosing MG patients with IIM complications. This model achieved an AUC of 0.94 for MG diagnosis and 0.70 for IIM diagnosis (Fig. 4B–E), indicating its efficacy in diagnosing patients with MG complicated by IIM.

The diagnostic potential of this model was further corroborated by DCA and calibration curve assessments. The DCA for the MG model indicated a beneficial threshold level from 0 to 0.85 (Fig. 4C), and the calibration curve exhibited a satisfactory fit, as evidenced

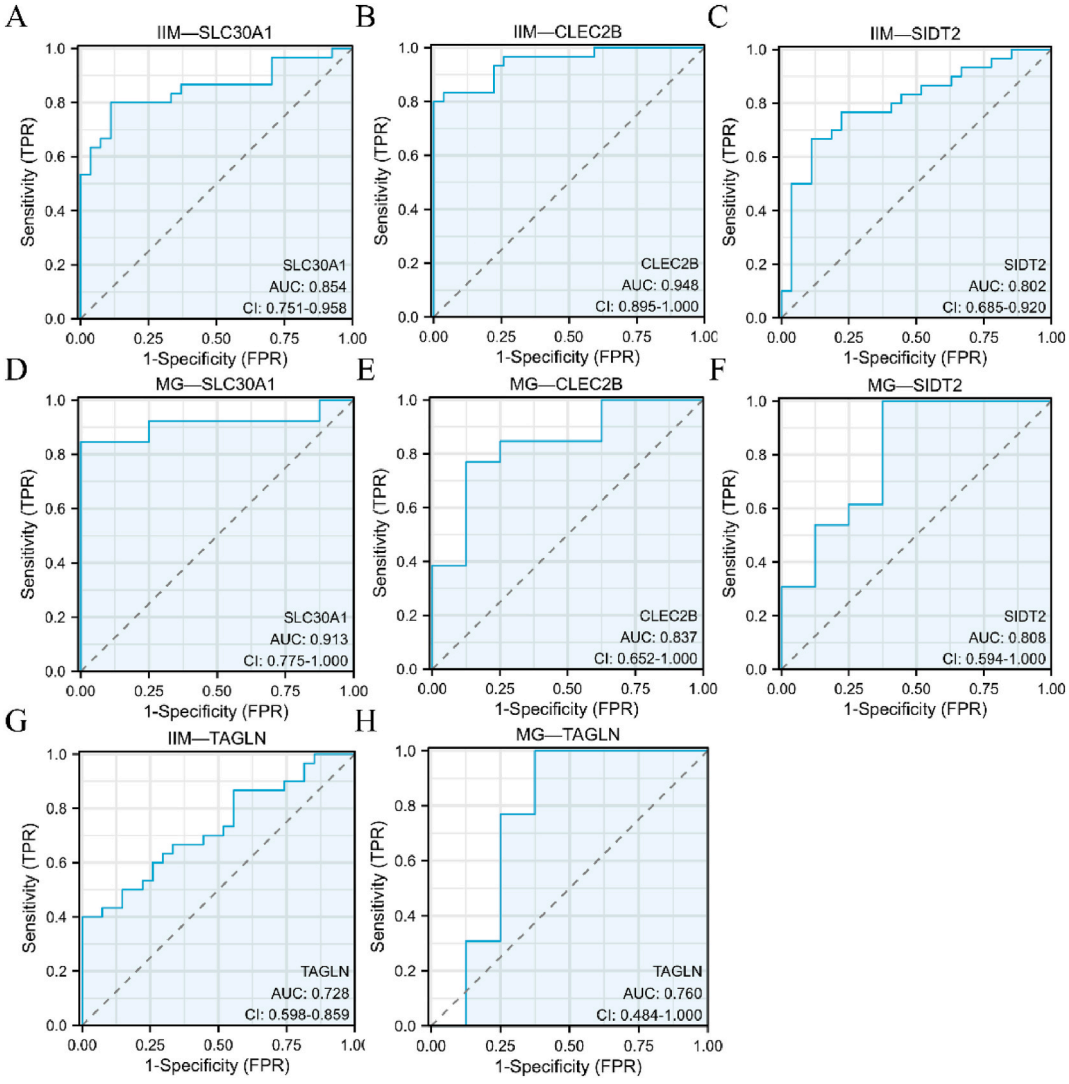


Fig. 3. A, B, C, G ROC analysis of co-DEGs for MG diagnosis; D, E, F, H ROC analysis of co-DEGs for IIM diagnosis.

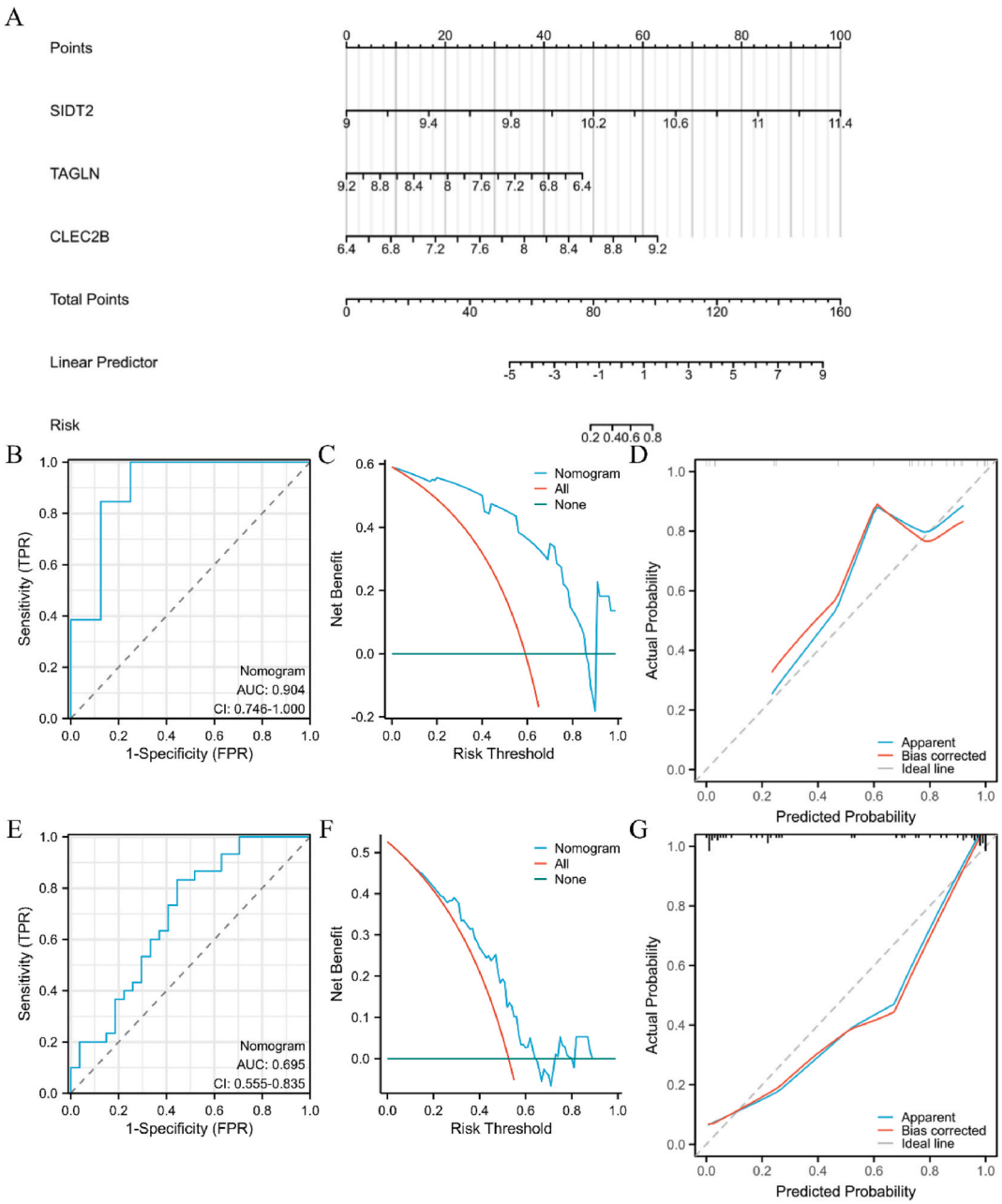


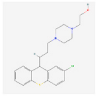
Fig. 4. A Nomogram prediction model for MG complicated with IIM; B ROC analysis of Nomogram prediction model for MG diagnosis; C DCA analysis of Nomogram prediction model for MG diagnosis (Threshold level for benefit 0–0.85); D calibration curve of Nomogram prediction model for MG diagnosis (chi-square goodness of fit test $P = 0.58$); E ROC analysis of Nomogram prediction model for IIM diagnosis; F DCA analysis of Nomogram prediction model for IIM diagnosis (Threshold level for benefit 0–0.64); G calibration curve of Nomogram prediction model for IIM diagnosis (chi-square goodness of fit test $P = 0.41$).

by a chi-square goodness-of-fit test P-value of 0.58 (Fig. 4D). In contrast, the DCA for IIM diagnosis revealed a benefit threshold level ranging from 0 to 0.64 (Fig. 4F), with the calibration curve yielding a chi-square test P-value of 0.41 (Fig. 4G). These findings suggest that the Nomogram prediction model, based on the identified co-DEGs, holds substantial clinical utility and accuracy in diagnosing MG patients with IIM complications. Consequently, this model is anticipated to serve as a valuable diagnostic tool in the clinical setting for patients with MG complicated by IIM.

3.6. Identification of candidate drugs

In this study, the Drug Signatures Database (DSigDB) accessible via the Enrichr platform was employed to systematically identify potential small molecular compounds that could serve as therapeutic agents for Myasthenia Gravis (MG) and Idiopathic Inflammatory Myopathies (IIM). Utilizing a data-driven approach, the top ten compounds were discerned based on their statistical significance, as indicated by their P-values. These compounds were methodically ranked and are comprehensively listed in Table 1. The array of drugs identified encompasses a diverse spectrum, including Decitabine, Parthenolide, Picrotoxinin, Phenobarbital, Camptothecin, Daunorubicin, TPEN, Zuclopenthixol, Scopolamine, and Chlorcyclizine. This assortment of molecular entities offers a promising avenue for the development of targeted therapies in the treatment of MG combined with IIM.

Table 1
The top ten potential small molecular compounds as therapeutic targets and treatments for MG and IIM.

Term	P-value	Combined Score	Genes	2D Structure[a]
Decitabine	0.000065408	701417.966558	TAGLN; CLEC2B; SLC30A1; SIDT2	
parthenolide	0.000336390	1065.242764	SLC30A1; SIDT2	
picrotoxinin	0.000565924	763.198682	SLC30A1; SIDT2	
phenobarbital	0.000687403	366.134462	TAGLN; SLC30A1; SIDT2	
camptothecin	0.000725197	649.827359	TAGLN; SLC30A1	
daunorubicin	0.000791625	613.727601	TAGLN; SLC30A1	
TPEN	0.000940435	548.231918	SLC30A1; SIDT2	
zuclopenthixol	0.000992834	529.020186	SLC30A1; SIDT2	
scopolamine	0.001976804	333.939218	SLC30A1; SIDT2	
chlorcyclizine	0.002797225	3012.374505	TAGLN	

[a] 2D structure from the STITCH database(http://stitch.embl.de/).

3.7. Identification of disease association

Employing the comprehensive DisGeNET database via the Enrichr platform, our research undertook a meticulous screening process to identify diseases potentially sharing genetic pathways with the co-DEGs found in Myasthenia Gravis (MG) and Idiopathic Inflammatory Myopathies (IIM). This systematic analysis revealed a notable genetic association between these co-DEGs and five specific diseases: Epidermodysplasia Verruciformis, Folic Acid Deficiency, Malignant Neoplasm of Lung, Lipoidosis, and Glomerulonephritis Membranoproliferative. These findings provide a compelling indication of shared genetic underpinnings between these conditions and MG/IIM, potentially unveiling new avenues for understanding their pathophysiology. graphically illustrates these associations, while delves into further detail regarding these genetic correlations.

4. Discussion

In this comprehensive study, we leveraged publicly available datasets and advanced bioinformatics tools to analyze the DEGs shared between MG and IIM. Our investigation successfully identified four DEGs common to both MG and IIM, providing evidence of a shared genetic foundation underlying these diseases. Further, we performed a detailed functional annotation of these DEGs, uncovering their involvement in a spectrum of biological processes and pathways. Notably, these processes include the release of signaling molecules, the negative regulation of neurotransmitter secretion and transport, as well as the import of calcium ions. This insight into the molecular mechanisms at play contributes significantly to our understanding of the pathogenesis of MG and IIM. The implications of our findings are substantial, offering potential avenues for the development of novel therapeutic strategies targeting these shared molecular pathways. Our research not only advances the genetic understanding of MG and IIM but also underscores the importance of integrative bioinformatics approaches in elucidating complex disease mechanisms.

This study identified four co-DEGs that were not previously reported in MG or IIM, indicating a unique molecular mechanism in MG with IIM complications. One of the identified genes, SIDT2, is a lysosomal membrane protein that is crucial in RNA and DNA uptake for lysosomal degradation [16]. Previous research has revealed that increased expression of SIDT2 can result in lysosomal dysfunction, a finding also observed in Alzheimer's disease [17]. Another gene identified, TAGLN, also known as SM22, belongs to the calcium family and serves as an actin-binding protein [18]. Past studies have linked TAGLN to unfavorable outcomes in various tumor types [19]. A recent study by Chanjun Sun et al. found that TAGLN promotes lung cancer progression by increasing IL6 levels [18]. Elevated IL6 levels have been associated with disease severity in IIM and MG in previous studies [20,21]. CLEC2B, a member of the C-type lectin domain family 2, is a protein encoded by CD69 located proximal to the natural killer gene complex, and highly expressed during lymphocyte activation [22]. CLEC2B has been linked to various tumor types and was found to regulate ferroptosis, impacting psoriasis progression [23–25]. Lastly, SLC30A1, a zinc transporter [26], was highly expressed in zebrafish infected with Pseudomonas aeruginosa in prior studies [27], suggesting its potential role in the immune response, similar to its action in MG complicated with IIM.

Our study identified several co-DEGs with potential diagnostic and therapeutic implications for MG and IIM. We constructed Nomogram prediction models based on the identified co-DEGs, which showed high predictive power for MG and could potentially serve as a diagnostic tool. The ROC analysis also indicated that targeting these co-DEGs may lead to the development of novel therapies against MG and IIM. In addition, the top ten small molecular compounds identified by the DSigDB library in Enrichr, such as Decitabine and parthenolide, may serve as potential therapeutic targets for MG and IIM. However, further experimental studies are needed to evaluate their efficacy and safety for treating these diseases.

Our comprehensive research delineates that the etiology of MG in conjunction with IIM is an intricate interplay of immunological factors. We have observed distinct patterns of immune cell infiltration in both MG and IIM, shedding light on their divergent yet intersecting pathogenic processes. Notably, an escalation in T cells gamma delta populations has been corroborated by prior investigations in both diseases [28,29]. This augmentation in T cells gamma delta intimates their pivotal role in the complexities of MG combined with IIM. Conversely, the modulation of activated Mast cells, a facet seldom addressed in preceding studies of IIM and MG, emerges as a significant factor in our findings. The altered activation levels of these cells are instrumental in the pathogenesis of MG when complicated by IIM. Further investigative efforts are imperative to comprehensively decipher these mechanisms and their implications for treatment strategies. Longitudinal studies encompassing extensive patient cohorts are essential for a more profound understanding of the dynamics of immune cell infiltration in these conditions. Additionally, an exploration into the molecular signaling pathways and genetic predispositions underpinning these immunological patterns could pave the way for novel therapeutic interventions and bespoke treatment approaches for patients with comorbid MG and IIM.

Moreover, based on the DisGeNET library in Enrichr, we identified five diseases that share common DEGs with MG and IIM, including Epidermodysplasia Verruciformis and Malignant neoplasm of the lung. These findings suggest a possible connection between these diseases, which may provide new directions for future research.

In conclusion, our study provides a comprehensive analysis of the co-DEGs and potential therapeutic targets for MG and IIM. Our findings may have important clinical implications for the diagnosis and treatment of these diseases, and may also contribute to a better understanding of the molecular mechanisms underlying their pathogenesis. However, further experimental validation is needed to confirm our results and to elucidate the precise roles of these DEGs in MG and IIM.

CRediT authorship contribution statement

Wenqu Yang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Feng**

Liang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Details of the contributions of individual authors

Their roles encompassed an extensive literature search, meticulous data extraction, comprehensive data analysis, and the drafting of the manuscript. The inception of the research theme was the brainchild of Wenju Yang and Feng Liang, who not only critically reviewed and amended the manuscript but also played a crucial role in securing the funding necessary for this research.

Data availability statement

This study been deposited into a publicly available repository. The data used are all from public databases.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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