Original Article

Signaling pathways of genetic variants and miRNAs in the pathogenesis of myasthenia gravis

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Background: Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disorder causing muscle weakness and characterized by a defect in synaptic transmission at the neuromuscular junction. The pathogenesis of this disease remains unclear. We aimed to predict the key signaling pathways of genetic variants and miRNAs in the pathogenesis of MG, and identify the key genes among them.

Methods: We searched published information regarding associated single nucleotide polymorphisms (SNPs) and differentially-expressed miRNAs in MG cases. We search of SNPs and miRNAs in literature databases about MG, then we used bioinformatic tools to predict target genes of miRNAs. Moreover, functional enrichment analysis for key genes was carried out utilizing the Cytoscape-plugin, known as ClueGO. These key genes were mapped to STRING database to construct a protein-protein interaction (PPI) network. Then a miRNA-target gene regulatory network was established to screen key genes.

Results: Five genes containing SNPs associated with MG risk were involved in the inflammatory bowel disease (IBD) signaling pathway, and *FoxP3* was the key gene. *MAPK1*, *SMAD4*, *SMAD2* and *BCL2* were predicted to be targeted by the 18 miRNAs and to act as the key genes in adherens, junctions, apoptosis, or cancer-related pathways respectively. These five key genes containing SNPs or targeted by miRNAs were found to be involved in negative regulation of T cell differentiation.

Conclusions: We speculate that SNPs cause the genes to be defective or the miRNAs to downregulate the factors that subsequently negatively regulate regulatory T cells and trigger the onset of MG.

Keywords: Myasthenia gravis (MG); polymorphism; miRNAs; signaling pathway; bioinformatics

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Introduction

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disorder causing muscle weakness and characterized by a defect in synaptic transmission at the neuromuscular junction. Currently, several autoimmune antibodies to acetylcholine receptors (AChR), muscle-specific kinase (MuSK), and low molecular weight receptor-related low-density lipoprotein-4 (Lrp4) have been demonstrated to attack the corresponding antigenic targets, leading to the onset of MG (1). However, the involved genetic and molecular mechanisms leading to the induction and production of these antibodies remain unclear.

A variety of genetic variants, e.g., –3279 and IVS9+459 in Foxp3, have been shown to be strongly associated with MG risk (2). Mutations in different genes encoding molecules important in the neuromuscular junction cause major changes in function (3). Nevertheless, several miRNAs, e.g., miR-122 and miR-185 (4) have been reported to be differentially expressed in the serum or peripheral blood mononuclear cells (PBMC) of MG patients, showing the close connections between these miRNAs and the pathophysiology of MG (5). Aberrant microRNA (miRNA) expression suggests that epigenetic modification influences MG risk (4).

Genes are the core of genetics and epigenetics. The overwhelming majority of associated genes are involved in the immune system. Therefore, we presumed that some key genes targeted by these genetic variants or miRNAs, i.e., at the DNA or RNA level, are involved in some critical pathways to trigger the onset of MG. By using bioinformatics tools, we aimed to predict these key genes and signaling pathways. We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/gs-20-39).

Methods

A summary of the following steps is shown in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Global search of SNPs and miRNAs in literature databases

To identify publications on MG and genetic variants, a comprehensive, systematic search of existing literature was first conducted. We searched the databases Medline, PubMed and Embase, up to June 1st 2019 using the MeSH terms "Myasthenia Gravis" and "Polymorphism, Single Nucleotide (SNP)", or "Genome-Wide Association Study (GWAS)". We performed another search of the literature on MG and miRNAs, using "Myasthenia Gravis" and "miRNAs" as MeSH terms. The search strategies used are listed in Table S1. All the identified publications were dealing with blood samples in MG cases and controls. We excluded articles without full text or not in English. Two studies collected data from these articles (KQ and YD, with 7 years and 12 years of experience in MG, respectively. YD has two years of statistical work experience. Both are familiar with English).

Prediction of miRNA target genes

Target genes of these miRNAs were predicted using the bioinformatics prediction tool "miRWalk" (http://www.umm.uni-heidelberg.de/apps/zmf/mirwalk/) (6) and validated by all the other tools provided on the miRWalk website including miRanda, miRDB, RNA22, and Targetscan.

Pathway enrichment analyses

In order to identify pathways involving the genes targeted by SNPs or miRNAs, we performed enrichment analysis using online functional annotation tools, i.e., DAVID (http://david.abcc.ncifcrf.gov/, updated in May 2018) (7) and STRING (http://string-db.org/, version 10.0) (8) The top most significant pathways were confirmed by gene counts ≥5, and both satisfied the Bonferroni-corrected cutoff (Bonferroni P value <0.05).

Analysis of protein-protein interaction networks

Protein-protein interaction networks (PPIs) and clusters of these proteins were verified by STRING (confidence scores ≥0.4). The key genes were defined as those with higher degrees of connectivity in PPIs. Cytoscape was utilized to construct the protein interaction network, which was used to calculate the score of gene nodes by using three centrality methods [i.e., Degree Centrality, Betweenness Centrality, and Closeness Centrality (9-11)]. The key genes were defined as those with higher degrees of connectivity in PPIs, which were identified by a network topology analysis (11,12).

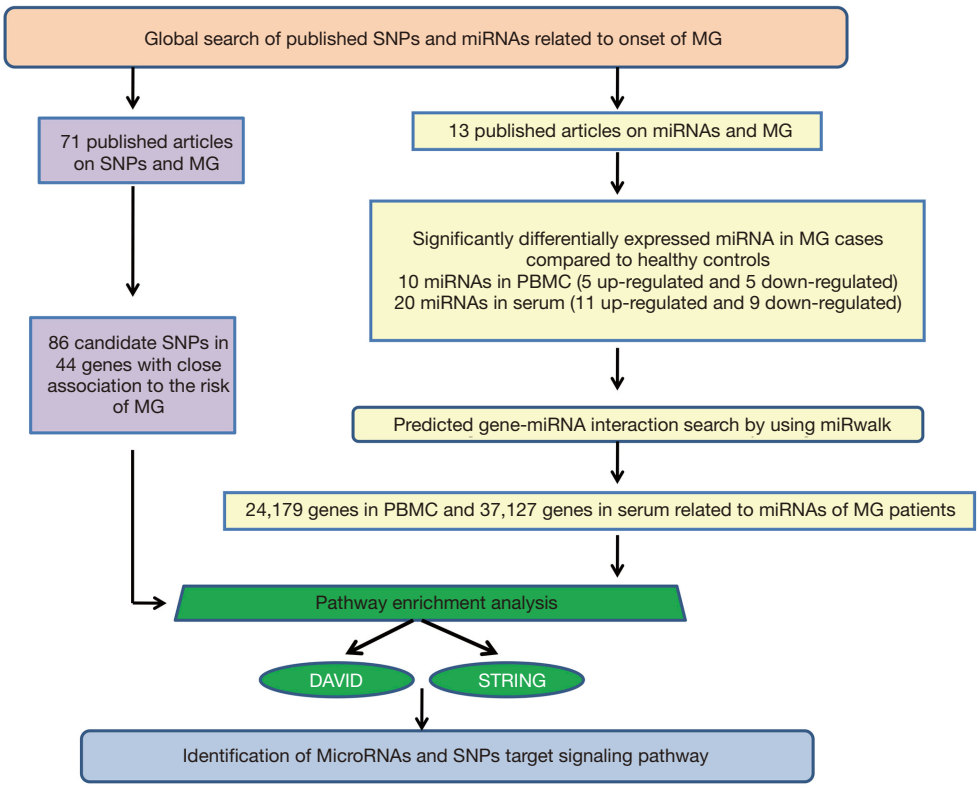

Figure 1 Flow chart of the strategy of the global search in PUBMED, target-gene prediction, KEGG pathway enrichment and protein–protein interaction (PPI) analysis.

Statistical analysis

Statistical analysis was carried out by using the MedCalc Statistical Software version v19.0.3 (MedCalc Software bvba, Ostend, Belgium). The key genes were defined as those with higher degrees of connectivity in PPIs, which were identified by a network topology analysis. The PathExNet tool was also used to isolate the genes that participate in each of the selected pathways based on KEGG 2019 along with the logFC and P value metrics, as provided by the differential expression analysis (13).

Results

We identified 86 candidate SNPs located in 44 related genes from 71 articles (Table S2) and 30 miRNAs from 13 articles (Table S3).

Five genes containing the reported SNPs associated with MG risk were involved in the inflammatory bowel disease (IBD) signaling pathway, and FoxP3 was the key gene

We used DAVID and STRING to identify signaling pathways of the 44 genes containing candidate SNPs (Table S1), and found these genes were involved in 15 signaling pathways (*Table 1*).

Cytoscape was utilized to construct the protein interaction network, which was used to calculate the score of gene nodes by using three centrality methods [i.e., Degree Centrality, Betweenness Centrality, and Closeness Centrality (9-11)]. Only one significant pathway was identified (gene counts =5, Bonferroni P value <0.040, and confidence scores =0.59), i.e., the IBD signaling pathway, involving five genes (Foxp3, IL6, IL10, IL1B, and TNF). Additionally, in these nodes with high degrees were

Table 1 The genes containing candidate SNPs were involved in 15 signaling pathways

Pathways	P value	P value FDR	P value bonferroni
1. Inflammatory bowel disease (IBD)	1.36E-08	5.02E-03	4.03E-02
2. African trypanosomiasis	8.18E-08	5.44E-03	9.25E-02
3. Malaria	3.23E-07	7.39E-03	1.33E-01
4. Cytokine-cytokine receptor interaction	7.40E-07	8.26E-03	1.64E-01
5. Pertussis	1.68E-06	8.26E-03	1.65E-01
6. Tuberculosis	2.13E-06	1.11E-02	2.40E-01
7. Rheumatoid arthritis	3.87E-06	1.11E-02	2.44E-01
8. Hematopoietic cell lineage	3.87E-06	1.15E-02	2.73E-01
9. Chagas disease (American trypanosomiasis)	6.29E-06	1.15E-02	2.75E-01
10. T cell receptor signaling pathway	6.83E-06	1.26E-02	3.30E-01
11. Amoebiasis	8.65E-06	1.26E-02	3.38E-01
12. Graft-versus-host disease	1.27E-05	1.26E-02	3.41E-01
13. Legionellosis	4.09E-05	1.40E-02	3.91E-01
14. NOD-like receptor signaling pathway	4.83E-05	1.41E-02	4.08E-01
15. Leishmaniasis	9.03E-05	1.68E-02	5.05E-01

FDR, false discovery rate.

identified using a network topology analysis, FoxP3 was shown to be the key gene among them (*Figure 2*, *Table 2*). This result suggests that the inflammatory and immune may play an important role in the occurrence and development of MG.

MiRNAs were involved in adherens junction, cancer-related and apoptosis pathways

We identified 24,179 and 37,127 genes as potential targets of the significantly differentially-expressed miRNAs in PBMC and serum, respectively (https://cdn.amegroups.cn/static/public/gs-20-39-01.docx).

In PBMC, 24,179 genes were found to be involved in 28 signaling pathways, but only one highly significant pathway, the adherens junction pathway (FC>0 and FC<0), had a Bonferroni P value <0.05 (*Table 3*). In serum, 37,127 genes were involved in 36 signaling pathways, and cancer-related pathway (FC<0) and apoptosis pathways (FC>0) seemed to be the most significant pathways among them (*Table 3*).

The adherens junction pathway consists of 46 interactions involving 15 genes (*Figure 3*), key genes including *mitogen-activated protein kinase 1* (*MAPK1*), *SMAD family member 4* (*SMAD4*), and *SMAD2* (*Figure 3*, *Table 3*).

In serum, the cancer-related pathway involved 67 genes and 379 interactions (*Figure 4*). However, it was too complicated to visualize these 379 interactions and identify the key genes, probably due to complicated variations and interactions of the genes involved in cancer biology. The apoptosis pathway involved 19 genes and 47 interactions (*Figure 5*). B-cell lymphoma 2 (BCL2) seemed to be the key gene among them (*Figure 5*).

The key genes targeted by SNPs and miRNAs are involved in negative regulation of T cell differentiation

We used STRING to reveal the possible biological processes of five key genes i.e., *BCL2*, *MAPK1*, *SMAD2*, *SMAD4* and *Foxp3* targeted by miRNAs or SNPs. Intriguingly, we found these key genes seemed to be involved in a pathway which negatively regulates T cell differentiation (*Figure 6*).

Discussion

We analyzed the mutational gene using bioinformatics, and found that Foxp3 was involved as the key gene in the signaling pathway of IBD, which is a chronic, relapsing

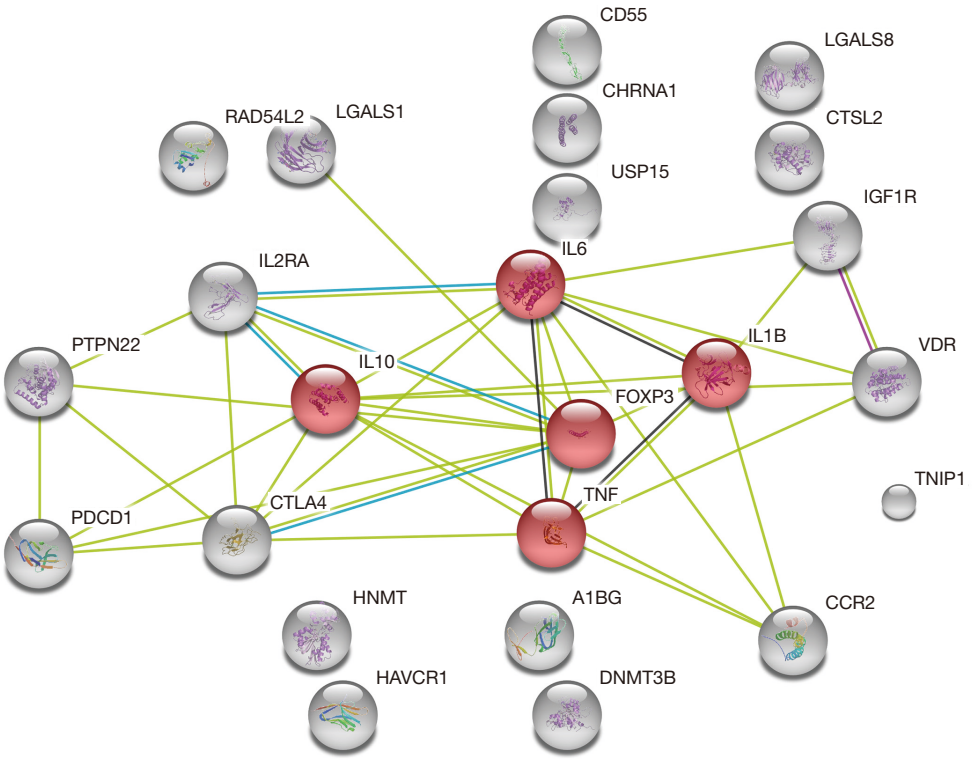

Figure 2 PPI analysis of 26 genes containing candidate SNPs related to high risk of MG. FoxP3 was shown to be the key gene. (Blue line: supported by database, yellow line: confirmed by experiment, red: closely-related genes, gray: unrelated genes).

Table 2 The degree centrality, betweenness centrality, and closeness centrality of the top five nodes in IBD signaling pathway

Gene	Degree	Betweenness	Closeness
Foxp3	13	3342.67	0.03264
IL6	11	3015.60	0.03069
IL1B	11	2900.16	0.03089
IL10	10	2917.63	0.03163
TNF	9	3011.86	0.03047

Degree, results of degree centrality algorithm; betweenness, results of betweenness centrality algorithm; closeness, results of Closeness centrality algorithm.

inflammatory disorder and an autoimmune disease. Concomitantly, some of the gene mutations found in this study are also mutated in IBD, such as TIM3, IL-10, IL-6, and TNF (14,15). Foxp3 regulates both the development and the function of CD4+CD25+ regulatory T cells (Tregs) (16). Tregs have been proven to control a variety of immune responses to maintain immune homeostasis, ranging from autoimmune diseases to inflammatory conditions (17).

In patients with MG, both the quantities and the functions of Tregs are significantly decreased, suggesting an important role of Tregs in the pathogenesis of MG (17). Tregs in MG patients show decreased expression of Foxp3 and IL-10 indicating a functional deficit. In patients with Foxp3 mutations, Tregs are absent or dysfunctional, always leading to severe autoimmune diseases, e.g., MG and IBD (18). Reduced Treg suppressive activity in MG patients is accompanied by elevated inflammatory cytokines

Table 3 Pathway analysis results and pathway related genes (Bonferroni-corrected probability value <0.05)

MiRNAs	Location	MiRNA's fold changes	Related genes	Pathways	P value	Bonferroni
miR-155 miR-146a miR-181c	PBMC	FC >0	*SMAD4*, IQGAP1, ACVR1B, ACVR1C, CTNND1, PTPRJ, SSX2IP, YES1*	Adherens junction	4.78E-3	4.88E-2
let-7a let-7b miR-145 let-7d let-7c	PBMC	FC <0	*SMAD2*, MAPK1*, WASF3, ACP1, ACTB, ACTG1, ACVR1B, ACVR1C, IGF1R, TJP1, TGFBR1, TGFBR2, YES1*	Adherens junction	3.00E-4	4.63E-2
miR-15b miR-122 miR-140-3p miR-185 miR-192 miR-20b miR-27a-3p miR-320a miR-855-5p miR-151a-3p miR-423-5p miR-409-3p miR-150-5p miR-21-5p let-7f-5p let-7d-3p let-7a-5p let-7f-5p miR-20b	Serum	FC <0	*VEGFA, TCF7, HIF1A , CCNE1, BCL2, CBL, E2F1, E2F3, FADD, GLI3, JAK1, KITLG, RAD51, RASSF5, TRAF5, XIAP, AR, AXIN2, BIRC5, BCR, CASP8, CCDC6, CUL2, CYCS, DVL1, DVL1L1, DVL3, EGLN1, EGLN3, FGFR1, FOXO1, FZD4, FZD6, GRB2, HDAC2, KBKB, ITGAV, IL8, LAMA3, LAMC1, MMP2, MAPK1, MAPK9, MAP2K1, MSH3, PPARG, PTEN, PIK3R1, PIK3R2, PIK3R3, PLD1, PDGFRA, PRKCA, RET, RB1, STAT3, TCF7L1, TGFBR2, AKT3, CRK, CRKL, RALB, VEGFC, WNT4, WNT5A, WNT7B, WNT8B*	Cancer related pathway	2.36E-04	4.39E-2
miR-15b miR-122 miR-140-3p miR-185 miR-192 miR-20b miR-27a-3p miR-320a miR-855-5p	Serum	FC <0	*BCL2*, FADD, XIAP, CHP2, CASP6, CASP7, CASP8, CYCS, IKBKB, IL1R1, IL3, IRAK2, MAP3K14, PIK3R1, PIK3R2, PIK3R3, PRKX, PRKACA, PRKAR2A, PPP3CA, PPP3R1, TNFRSF10A, TNFRSF10D*	Apoptosis	5.45E-04	4.85E-2

FC, Fold changes: expressions of miRNAs in PBMC or serum in between MG patient and normal control. *, leader genes.

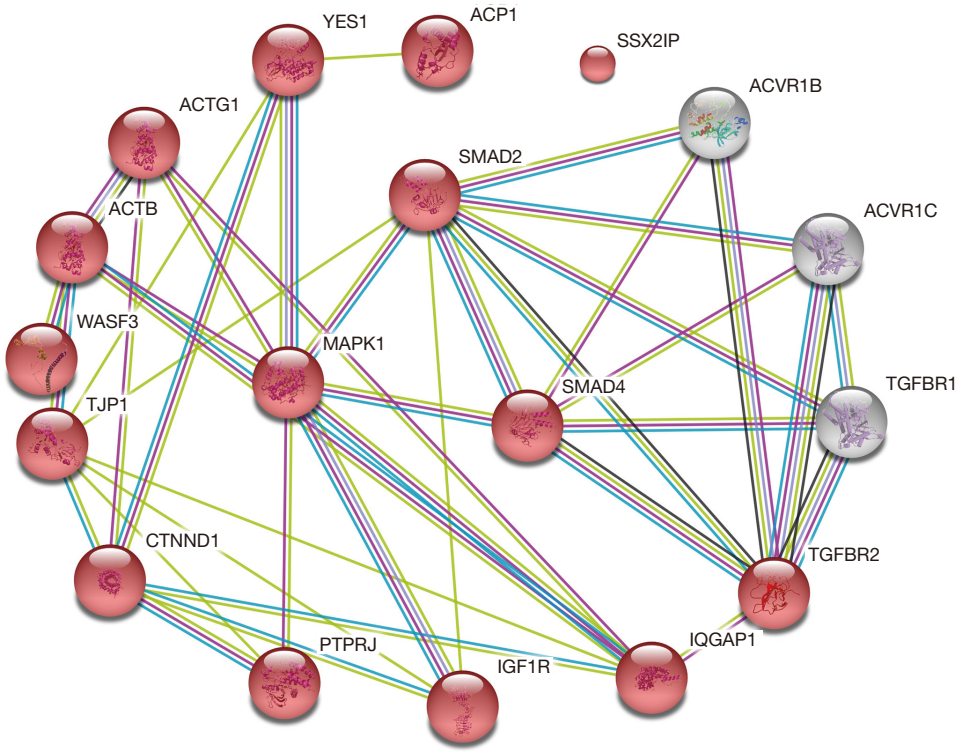

Figure 3 Genes targeted by the differentially-expressed miRNAs in PBMC of MG are involved in the adherens junction pathway (Blue line: supported by database, yellow line: confirmed by experiment, red: closely-related genes, gray: unrelated genes).

(IL-6, IL-17, TNF-α, and IL-1β), most of which are normally suppressed by Tregs (19). Immunomagnetically-purified Tregs from MG patients were found to suppress the proliferative response of other T cells (20). Leading to imbalance of T/B cells and subsequently affecting the production of auto antibodies (21,22). Additionally, differentiation of Tregs is anticipated to be associated with myasthenia predisposition (23). Overall, the mechanisms of the IBD pathway in MG are unclear, but we speculate that at the DNA level, mutations of Foxp3 apply to Tregs, leading to severe autoimmune diseases via the IBD signaling pathway.

Recent study reveals that imbalance in T follicular helper cells (Tfh) producing IL-17 promotes proinflammatory responses in myasthenia gravis (24). The ratio of Tfh17/Tfh1 has been shown to correlate with a pro-inflammatory and enhanced humoral immune response (25). Preite found that reconstitution of lymphopenic mice with CXCR5-sufficient and CXCR5-deficient Treg cells, as well as non-regulatory memory CD4 T cells, restrained expansion of Tfh and germinal center B cells, and restored germinal center B-cell dynamics and generation of highly mutated, high-affinity antibodies (26). In summary, in the occurrence and development of MG, Tregs control a variety of immune responses to maintain immune homeostasis, ranging from autoimmune diseases to inflammatory conditions (17).

The miRNAs play crucial roles in controlling and modulating immunity (27). Thus far, epidemiology studies have revealed miRNAs differentially expressed in patients with MG (Table S2); however, the target genes and related pathways remain unclear. We used bioinformatics tools to predict target genes and potential pathways of these miRNAs. Our study identified three critical pathways in the onset of MG, including one pathway in PBMC, the adherens junction signaling pathway, and two pathways in serum, the apoptosis and cancer-related pathways.

The adherens junction signal pathway is a key player in the establishment and maintenance of apical-basal cell polarity, regulation of cell proliferation, mobility, and differentiation (28). However, our study found that the differentially-expressed miRNAs in MG may be involved in the adherens junction pathway, in which MAPK1, (also

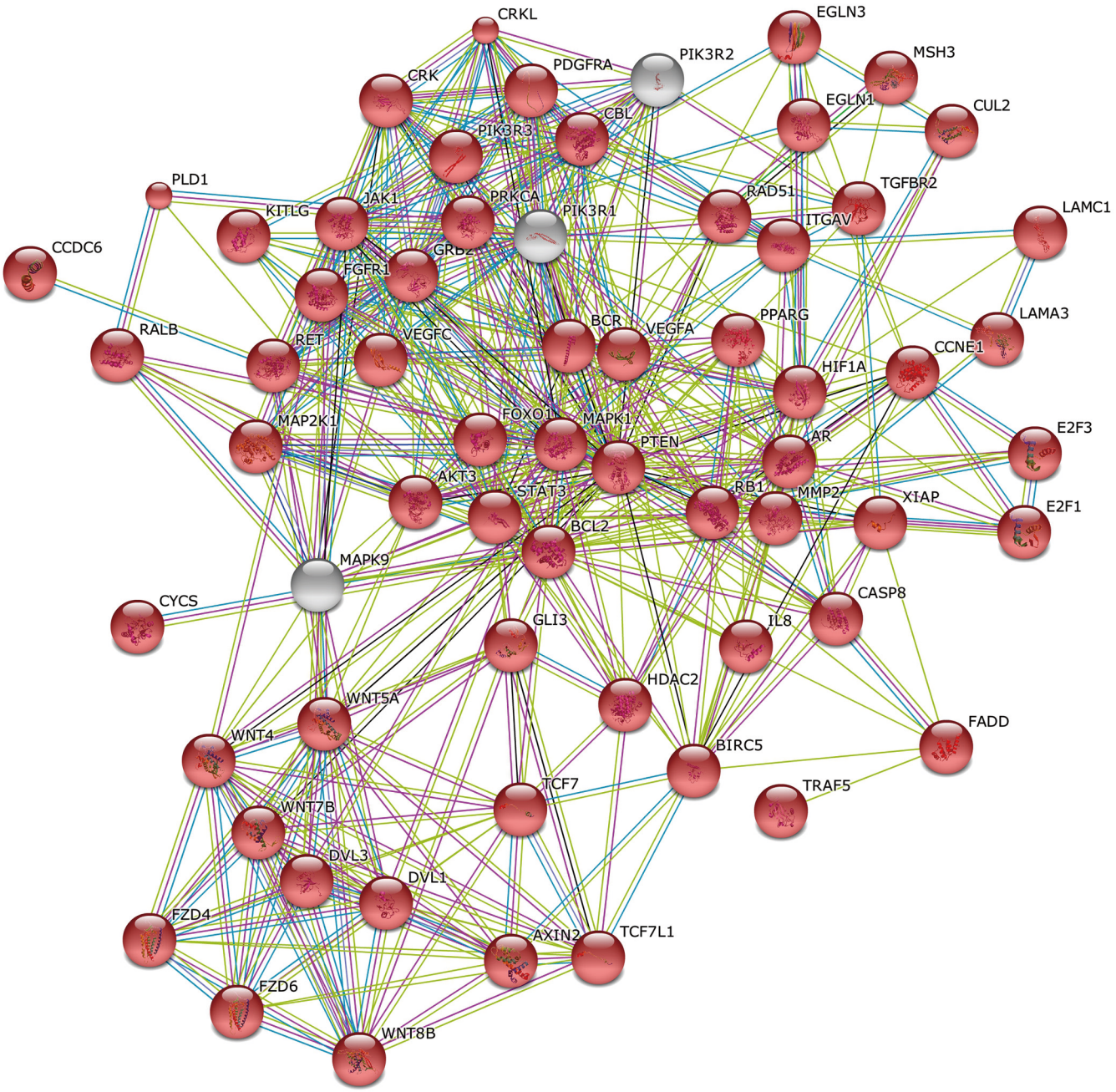

Figure 4 Genes targeted by the differentially-expressed miRNAs in serum were associated with cancer-related pathways (Blue line: supported by database, yellow line: confirmed by experiment, red: closely-related genes, gray: unrelated genes).

known as Erk2), SMAD 2 and 4 are the key genes. MAPK1 is essential to the signal transduction of extracellular stimuli from the membrane to the nucleus (29). Indeed, the amount of MAPK1 in MG serum was 11.5 times less than in controls (30). In addition, SMADs can activate intracellular TGF-β1 (31). Thereafter, the activated TGF-β1 can induce the generation of CD4+Foxp3+ Tregs (32) and suppress proliferation of AChR-reactive T cells (32). Although the underlying mechanisms of MAPK1, SMAD2, and SMAD4 in the adherens junction pathway during the onset of MG

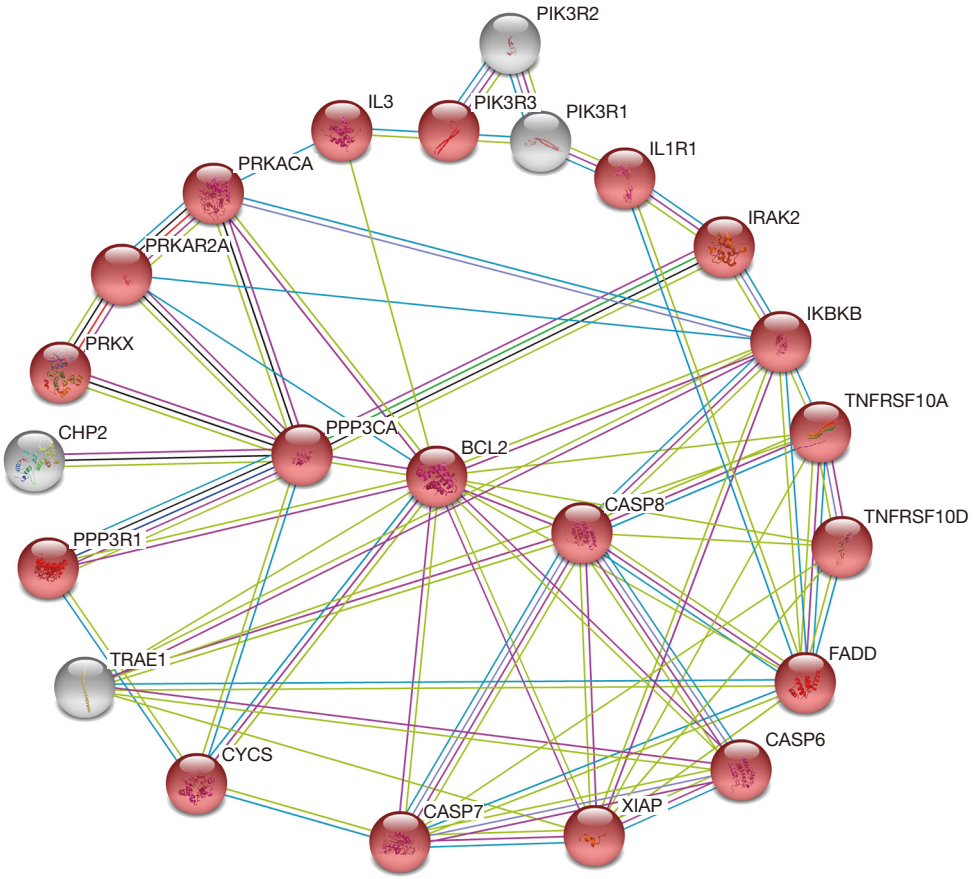

Figure 5 Genes targeted by the differentially-expressed miRNAs in serum showed a relationship with apoptosis (Blue line: supported by database, yellow line: confirmed by experiment, red: closely-related genes, gray: unrelated genes).

remain unclear, the relationship between this pathway and Tregs warrants further study.

Apoptosis plays an important role via Fas cascades in the onset of many other autoimmune diseases, as well as MG (33). The BCL2 gene located at chromosome 18q21, encodes a 26-kD protein which is an apoptosis inhibitor (34). In thy0517 thymoma cells, BCL2 was found to be overexpressed (35). High expression of BCL2 may cause inhibition of apoptosis in thymocytes, and potentially induce the occurrence of thymoma (36). Although there is no evidence to prove the relationship between MG and BCL2, in another autoimmune disease, systemic lupus erythematosus (SLE), the expression of BCL2 may confer survival and proliferative advantages on Tregs and could represent a possible marker of SLE disease severity (37). Another study revealed that T cell-specific expression of a BCL2 mutant transgene results in enhanced rescue of thymocytes from negative selection, increasing development of Tregs (38). From these findings, we speculate that BCL2 plays an important role in apoptosis signaling through Tregs.

In summary, our study revealed that IBD, adherens junction, apoptosis, and cancer-related signaling pathways are probably involved in the pathogenesis of MG. Intriguingly, all the key genes targeted by SNPs or miRNAs, i.e., *Foxp3*, *SMAD2*, *MAPK1*, *SMAD4*, and *BCL2*, seemed to be involved in negative regulation of T cell differentiation. Based on these findings, we hypothesized that SNPs cause the genes to be defective or the miRNAs to down regulate the factors that subsequently negatively regulate Tregs and trigger the onset of MG (*Figure 6*). Tregs are the core of MG pathogenesis. However, the studies analyzed describe the results from a diverse range of MG cases at different times after onset. The SNPs or miRNAs could also be the results of an immune response to an ongoing insult, immunosuppressive agent or thymus

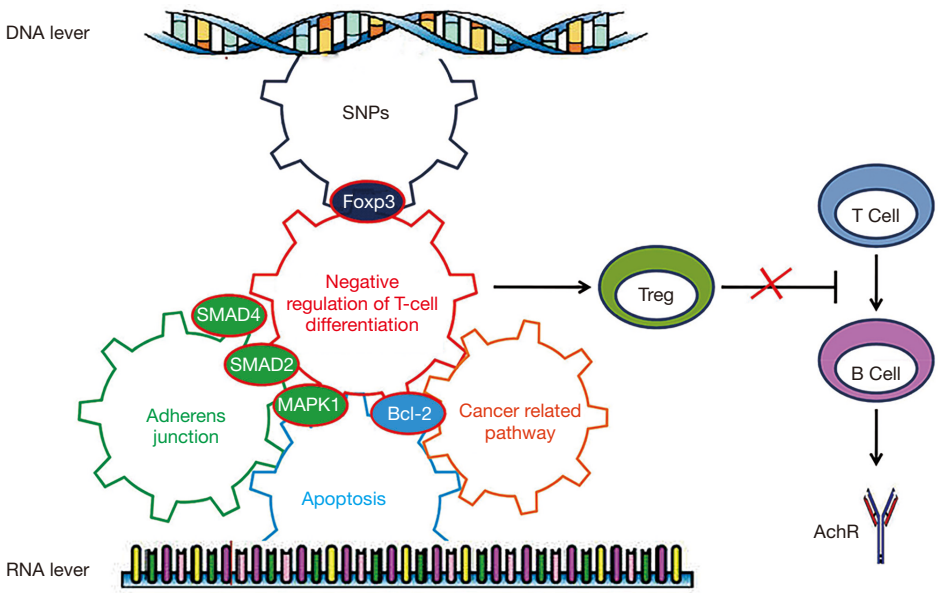

Figure 6 Five key genes *Foxp3*, *MAPK1*, *SMAD2*, *SMAD4*, and *BCL2*, are involved in negative regulation of T cell differentiation. We speculate that SNPs cause the genes to be defective or the miRNAs to down-regulate factors that subsequently negatively regulate Tregs and trigger the onset of MG.

pathology. Therefore, our hypothesis and the underlying mechanisms warrant further robust study.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at http://dx. doi. org/10. 21037/gs-20-39

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx. doi. org/10. 21037/gs-20-39).The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 The search strategies in PubMed

("Myasthenia Gravis"[Mesh] OR (((((("myasthenia gravis"[MeSH Terms] OR ("myasthenia"[All Fields] AND "gravis"[All Fields]) OR "myasthenia gravis"[All Fields]) AND Ocular[Title/Abstract]) OR Ocular Myasthenia Gravis[Title/Abstract]) OR (("myasthenia gravis"[MeSH Terms] OR ("myasthenia"[All Fields] AND "gravis"[All Fields]) OR "myasthenia gravis"[All Fields]) AND Generalized[Title/Abstract])) OR Generalized Myasthenia Gravis[Title/Abstract])) AND ((((((((((((((((MicroRNA[Title/Abstract] OR miRNAs[Title/Abstract]) OR Micro RNA[Title/Abstract]) OR (("rna"[MeSH Terms] OR "rna"[All Fields]) AND Micro[Title/Abstract])) OR miRNA[Title/Abstract]) OR Primary MicroRNA[Title/Abstract]) OR (("micrornas"[MeSH Terms] OR "micrornas"[All Fields] OR "microrna"[All Fields]) AND Primary[Title/Abstract])) OR Primary miRNA[Title/Abstract]) OR (("micrornas"[MeSH Terms] OR "micrornas"[All Fields] OR "mirna"[All Fields]) AND Primary[Title/Abstract])) OR pri-miRNA[Title/Abstract]) OR pri miRNA[Title/Abstract]) OR (("rna"[MeSH Terms] OR "rna"[All Fields]) AND Small Temporal[Title/Abstract])) OR (Temporal[All Fields] AND ("rna"[MeSH Terms] OR "rna"[All Fields]) AND Small[Title/Abstract])) OR stRNA[Title/Abstract]) OR Small Temporal RNA[Title/Abstract]) OR pre-miRNA[Title/Abstract]) OR pre miRNA[Title/Abstract]) AND "MicroRNAs"[Mesh])
((((("Myasthenia Gravis"[Mesh]) OR ((((Myasthenia Gravis, Ocular[Title/Abstract]) OR Ocular Myasthenia Gravis[Title/Abstract]) OR Myasthenia Gravis, Generalized[Title/Abstract]) OR Generalized Myasthenia Gravis[Title/Abstract]))) AND (("Polymorphism, Genetic"[Mesh]) OR ((((Polymorphisms, Genetic[Title/Abstract]) OR Genetic Polymorphism[Title/Abstract]) OR Polymorphism (Genetics)[Title/Abstract]) OR Genetic Polymorphisms[Title/Abstract]))))
((((("Myasthenia Gravis"[Mesh]) OR ((((Myasthenia Gravis, Ocular[Title/Abstract]) OR Ocular Myasthenia Gravis[Title/Abstract]) OR Myasthenia Gravis, Generalized[Title/Abstract]) OR Generalized Myasthenia Gravis[Title/Abstract]))) AND (("Polymorphism, Single Nucleotide"[Mesh]) OR ((((((Nucleotide Polymorphism, Single[Title/Abstract]) OR Nucleotide Polymorphisms, Single[Title/Abstract]) OR Polymorphisms, Single Nucleotide[Title/Abstract]) OR Single Nucleotide Polymorphisms[Title/Abstract]) OR SNPs[Title/Abstract]) OR Single Nucleotide Polymorphism[Title/Abstract]))))
((((("Myasthenia Gravis"[Mesh]) OR ((((Myasthenia Gravis, Ocular[Title/Abstract]) OR Ocular Myasthenia Gravis[Title/Abstract]) OR Myasthenia Gravis, Generalized[Title/Abstract]) OR Generalized Myasthenia Gravis[Title/Abstract]))) AND (("Genome-Wide Association Study"[Mesh]) OR ((((((((((((((((Association Studies, Genome-Wide[Title/Abstract]) OR Association Study, Genome-Wide[Title/Abstract]) OR Genome-Wide Association Studies[Title/Abstract]) OR Studies, Genome-Wide Association[Title/Abstract]) OR Study, Genome-Wide Association[Title/Abstract]) OR Genome Wide Association Scan[Title/Abstract]) OR Genome Wide Association Studies[Title/Abstract]) OR GWA Study[Title/Abstract]) OR GWA Studies[Title/Abstract]) OR Studies, GWA[Title/Abstract]) OR Study, GWA[Title/Abstract]) OR Whole Genome Association Analysis[Title/Abstract]) OR Whole Genome Association Study[Title/Abstract]) OR Genome Wide Association Analysis[Title/Abstract]) OR Genome Wide Association Study[Title/Abstract]))))

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Table S2 Reported SNPs and genes related to MG risk

PMID	Authors	Gene	Genotype	Ethnic group or descent	Cases	Healthy controls	Odds ratio (95% CI) or other results
28364296	Yu Hong (39)	*AIRE*	rs3761389	Chinese	114 Adult MG (18–40 years)	487	P=0.01, CI: 1.38 (1.07–1.78)
28364296	Yu Hong (39)	*CTLA-4*	rs231775	Chinese	114 Juvenile MG (1–18 years)	487	P=0.02, CI:0.64 (0.44–0.93)
28364296	Yu Hong (39)	*CTLA-4*	rs733618	Chinese	114 Juvenile MG (1–18 years)	487	P=0.005, CI:1.60 (1.15–2.22)
28364296	Yu Hong (39)	*CHRNA1*	rs16862847	Chinese	114 Juvenile MG (1–18 years)	487	P=0.03, CI:2.04 (1.06–3.90)
28364296	Yu Hong (39)	*CHRNA1*	rs2229957	Chinese	114 Juvenile MG (1–18 years)	487	P=0.0005, CI:2.64 (1.50–4.63)
28364296	Yu Hong (39)	*CHRNA1*	rs16862847	Chinese	207 Adult MG (18–40 years)	487	P=0.006, CI:2.03 (1.21–3.41)
10606977	Xu BY (40)	*ADRB2*	Arg/Arg	Swedish	145MG (Ocular =10; Generalized =135)	96 HC	P=0.0022 OR=3.60 (1.52–8.54)
10606977	Xu BY (40)	*ADRB2*	Gly/Gly	Swedish	145MG (Ocular =10; Generalized =135)	96 HC	P=0.0079 OR=0.45 (0.26–0.81)
10606977	Xu BY (40)	*ADRB2*	Carriage of Gly	Swedish	145MG (Ocular =10; Generalized =135)	96 HC	P=0.0022 OR=0.27 (0.12–0.66)
27338803	Wang L (41)	*ADRB2*	–	–	27 MG	–	P=0.041
1352699	Degli-Esposti MA (42)	*BAT1*	8.1 ancestral haplotype (HLA A1, Cw7, B8, BfS, C4AQ0, C4B1, DR3, DQw2)	Caucasoid	16 MG	16 adult Caucasoid subjects from Busselton	RR =5.5
19513280	Kim HS (43)	*CCR2*	rs1799864	Korean	109MG	115	P<0.05
11857062	Wang XB (44)	*CTLA4*	+49 A/G	Sweden	15 MG(+) Thymoma 30 MG(+) thymic hyperplasia 11 MG(+) normal thymus	122	Thymoma *vs.* normal and hyperplastic thymic: 8.44 (1.77–40.4)
16178018	Chuang WY (45)	*CTLA4*	+49A/G	German	79 MG(+) thymoma	46 MG(-) thymoma	129 non-thymoma EOMG
18088253	Wang XB (46)	*CTLA4*	-1772T/C -1661A/G	Sweden	165 MG	148	1.87 (1.01–3.49)
24373506	Chuang WY (47)	*CTLA4*	+49A/G	Caucasian	116 LOMG patients	172	P=0.0029,2.7(1.7-4.0)
19345707	Fernández-Mestre M (48)	*CTLA4*	49 A/G	Venezuelans	46 MG	98 HC	P>0.05
18595775	Gu (49)	*CTLA-4*	RQ sCTLA-4/(RQ sCTLA-4 + RQ mCTLA-4)	Swedish Caucasian	52 MG patients	31healthy individuals	P<0.05
12225905	Wang XB (50)	*CTLA-4*	(AT)n polymorphism in the 3'-untranslated region	Swedish Caucasian	96 AChR(+) MG patients	100 ethnically matched healthy individuals	p<0.0001; r=0.396,
25643325	Renton AE (51)	*CTLA4*	rs231770	white individuals from North America; Italian cases	1032acetylcholine receptor antibody–positive myasthenia gravis	1998 healthy individuals	1.37; 95% CI, 1.25-1.49
25643325	Renton (51)	*TNFRSF11A*	rs4263037	white individuals from North America	the late-onset cases in 1032 acetylcholine receptor antibody-positive myasthenia gravis	1998 healthy individuals	1.41; 95% CI, 1.29-1.53
25003519	Sun L (52)	*CTLA4*	rs1863800 rs733618 rs231775	Chinese	168 patients with MG	233 healthy controls	ROCAUC value:0.570;CI:0.513-0.626 ROCAUC value:0.580;CI:0.523-0.638 ROCAUC value:0.568;CI:0.512-0.625
11426323	Ligers A (53)	*CTLA4*	–318C/C	Sweden	29 MG	26 HC	P<0.05
11574100	Franciotta D (54)	*C4A*	C4A/Q0	Italian	81 MG	100 HC	P<0.05, RRs2.2 *vs.* controls(MG female)
11574100	Franciotta D (54)	*HLA*	DRB1 03	Italian	81 MG	100 HC	P<0.005, RRs7.8 *vs.* controls(MG female)
11574100	Franciotta D (54)	*TNFB*	TNFB 1	Italian	81 MG	100 HC	P<0.05, RRs7.0 *vs.* controls(MG female)
20942939	Ramanujam R (55)	*CIITA*	rs3087456	Swedish	446 MG patients	1866 HC	P=0.092; 0.86 (0.73-1.02)
7910962	Garchon HJ (56)	*CHRNA*	HB*14 allele	Caucasian	81 generalized MG	100 MG	P<0.0002
17687331	Giraud M (57)	*CHRNA1*	rs16862847	French United kingdom	330 EOMG	260	EOMG: 2.19(1.41-3.39)
14735155	Giraud M (58)	*CHRND*	268 allele	French	350 MG	168	thymoma(-)MG: 1.78 (1.037– $+\infty$) anti-titin (-)MG:2.07 (1.16– $+\infty$)
17869649	Viken MK (59)	*CTSL2*	rs4361859	German	83 MG patients 31 EOMG	244 HC	EOMG OR = 1.82, 95% CI: 1.07–3.12, P= 0.03
19675582	JM Heckmann (60)	*DAF*	rs28371586	African	139 EOP	167	8.6 (2.8–26.1)
22744667	Landouré G (61)	*ENOX1*	D13S219 - D13S326	–	Seven family members (4 MG, 2 unaffected, and 1 with uncertain diagnosis)	764	$P < 0.001$
14597109	van der Pol WL (62)	*FCGR2A*	FcγRIIa-R/R131	Dutch	107 MG patients	239 HC	P<0.01;2.4, 95% CI1.4–3.9
9521619	Raknes G (63)	*FCGR2A*	FcgRIIA-H/H	Norwegian Caucasians	30 MG	49 HC	P=0.02
23228687	Zhang JM (64)	*FOXP3*	IVS9+459 rs2280883	Chinese	118 MG	124	MG(+): 0.44 (0.25–0.79)
19693092	Chuang WY (65)	*PTPN22*	+1858C/T	German	79 MG(+) thymoma 46 MG(-) thymoma 129 non-thymoma EOMG	172	MG(+) thymoma: 2.66(1.38–5.12) EOMG: 2.81(1.58–5.00)
19406179	Greve B (66)	*PTPN22*	+1858C/T	German Hungary	50 anti-titin (+) non-thymoma MG	379	anti-titin (+) non-thymoma MG: 2.10 (1.23–3.58)
18533277	Lefvert (67)	*PTPN22*	W620 variant	Swedish	409MG	1557	1.52 (1.21–1.90)
25119822	Gizem A.Kaya (68)	*PTPN22*	rs2476601	Turkey	231AChR-MG	293	2.5 (1.2–5.1)
16437561	Vandiedonck C (69)	*PTPN22*	rs2476601	French	470293 nonthymoma patients without anti-titin 293	296	thymoma(-)anti-titin(-)1.97 (1.32–2.97)
22197427	Provenzano (70)	*PTPN22*	rs2488457	Caucasian	356MG	439 healthy individuals	2.10 (1.13–3.89)
26318187	Xiong X (71)	*PTPN22 R620W*	–	Hungary, France, Italy, Turkey, Sweden, Germany (Caucasian)	2802 cases	3730 controls	Overall: (OR=1.57; 95% CI, 1.34–1.82; I^2=31%) EOMG (OR=2.38; 95% CI, 1.52–3.71; I^2=0%) Thymoma: (OR=1.59; 95% CI, 1.28–1.98; I^2=0%)
23076337	Zheng J (72)	*PTPN22*	C1858T		1286 MG	2404 HC	OR=1.53; 95% CI:1.31–1.80, P =1.09 $\times 10^{-7}$)
23055271	Gregersen PK (73)	*PTPN22*	rs2476601	North European	649 EOMG	2596 HC	OR =1.71, P=8.2$\times 10^{-10}$; 95% CI:1.44–2.02
23055271	Gregersen PK (73)	*TNIP1*	rs2233287 rs4958881	North European	649 EOMG	2596 HC	EOMG rs2233287: 1.73 (1.44–2.08) rs4958881: 1.71 (1.44–2.02)
23055271	Gregersen PK (73)	*HLA class I region*	rs7750641	North European	649 EOMG	2596 HC	P= 1.2$\times 10^{-92}$, OR =6.25 (95% CI: 4.89–6.85)
17509455	Yilmaz V (74)	*IFNG*	+874T	Mixed	115 patients AChR (+)=92 ATA (+)=32	204 HC	MG: P=0.012, OR =0.5, 95% CI: 0.29–0.86 AChR (+): P=0.01, OR =0.47, 95% CI: 0.27–0.84 ATA (+): P=0.014, OR = 0.36, 95% CI: 0.16–0.79
17509455	Yilmaz V (74)	*IL10,*	-2763A	Mixed	115 patients AChR (+)=92	204 HC	MG: P=0.049, OR =1.69, 95% CI:1–2.85 AChR (+): P=0.036, OR =1.83, 95% CI: 1.04–3.25
25118158	Lili Yang (75)	*IGF1R*	rs28457673	Chinese	18MG	93	Bioinformatics
22119518	Pál Z (76)	*I75V(IL-4R)*	rs1805010	Caucasian	214AChR(+)MG	299	1.77 (1.1–2.84)
11777547	Sciacca FL (77)	*IL1A*	-889C/C	Italian	421MG	995	associated with EOMG (P=0.0044) in the whole MG group
9521608	Huang D (78)	*IL1B*	IL-1β TaqI RFLP(A2/A2)	Swedish caucasian	107 MG patients Thymoma=16.8%; Hyperplasia= 38.3%; Normal =13.1%; UnTx= 31.8%	82 ethnically matched healthy individuals	The frequency of the genotype A2/A2 was significantly increased (P=0.010, Pc=0.030)
10580802	Huang D (79)	*IL6*	-174A/D	Caucasian	141MG	127	OR=17, p<0.0001
10376939	Huang DR (80)	*IL10*	134 G/G	Caucasian	149 MG	109	24 thymoma (+) 3.60 (1.80–7.21)
10376939	Huang DR (80)	*IL10*	IL10.G, allele 134	Swedish Caucasian	149 patients, 97 patients were thymectomized and 24 had thymoma, 51 hyperplasia and 22 normal thymic histology	109 ethnically matched healthy invididuals	P=0.0004, pc=0.0192, OR=3.60, 95% CI:1.80–7.21
23049601	Zagoriti Z (81)	*IL-10*	-	Greeks	101 MG	101 HC	P= 0.068
19299022	Alseth EH (82)	*IL-10*	ACC/ACC ACC/ATA	Norwegian Caucasians	64 MG patients	87 HC	P=0.05 P=0.03
26337284	Yue YX (83)	*IL-17*	rs2275913	Han Chinese population	480 MG patients	487 controls	P=0.428; CI, 10.76(0.898-1.289)
20728947	Pal Z (84)	*LGALS1* *IL2RB*	rs4820293 rs4820294 rs743777 rs228941 rs3748067	Hungary	146 MG	291	9.2 (95% CI N.S) P=0.021
22683700	Pál Z (85)	*LGALS8*	rs2737713	Caucasian	149MG, 214RA and 134 repetitive cohorts	365	anti-AChR (+) MG with RA 3.87 (1.7-8.72)
23932992	Kellermayer B (86)	*HNMT*	A939G	Caucasian	213 MG（Anti-AchR+= 140; Anti-Titin+=41）	342 HC	(AchR+) P=0.05; 0.67 (0.44–0.95) (Anti-Titin+) P=0.004; 0.54 (0.35–0.84)
22521184	Najiba Fekih-Mrissa (87)	*HLA-DRB1* *HLA-DQB1*	DRB1*04. DRB1*03, DRB1*04, DQB1*02, DQB1*03	Tunisian patients	48 MG patients(37.5% have thymoma)	100 healthy controls	HLA-DRB1*03 (pc <10^{-3}), DRB1*04 (pc = 0.005), DQB1*02 (pc = 0.002) and, DQB1*03 (pc =0.007)
22503410	Zhu WH (88)	*HLA-DQA1* *HLA-DQB1*	DQA1*03:02 DQB1*03:03:02	Southern Han Chinese	205 MG patients	100 HC	childhood-onset ocular MG P≤0.0001, OR=17.8
21917268	Yang H (89)	*HLA-DQA1* *HAL-DQB1*	DQA1*0103 DQB1*0601	Northern Han Chinese	84 MG patients	293 HC	P=0.000, OR:0.24, 95% CI: 0.13–0.49 P=0.001, OR:0.40, 95% CI: 0.22–0.50
23091703	Testi M (90)	*HLA-DQB1*	DQB1*05:02	Italian patients	28 (absence of thymoma, the presence of AChR and LOMG)	100 healthy controls	pc = 0.0228
19490212	Hajeer AH (91)	*HLA-A*	HLA-B*08	Saudi	109 MG HLA-B*08=65	383 HC	OR:2.51;95% CI: 1.64–3.83; P=0.00001
19561379	Yousefipour GA (92)	*HLA-DQA1* *HLA-DQB1*	DQA1*0101/2 DQB1*0502	sporadic patients	104MG	816 healthy controls	pc =1.69 pc =2.41
16720217	Saruhan-Direskeneli G (93)	*HLA-DQA1* *HLA-DQB1*	DQA1*0103 DQB1*0502	Caucasian	132 MG (AChR antibody(+)=107, AChR antibody(-)=25)	250 healthy unrelated individuals (143 women and 107 men)	DQA1*0103 (OR: 0.5) DQB1*0502 (OR: 1.9)
27181991	Saruhan-Direskeneli G (3)	*HLA class I region*	rs113519545	Turkic	211 EOMG	541HC	P=2.24$\times 10^{-16}$, CI,5.71(3.77-8.66)
27181991	Saruhan-Direskeneli G (3)	*HLA class II region*	rs111256513	Turkic	109 LOMG	541HC	P=2.48$\times 10^{-6}$, CI,2.22(1.59-3.09)
27181991	Saruhan-Direskeneli G (3)	*HLA-DQB1*	rs68081734	Turkic	78 MuSK-MG	541HC	P=2.25$\times 10^{-14}$, CI,5.86(3.72-9.22)
8964894	Hjelmström P (94)	*HLA-DQB1*	DQB1*0201	Caucasian	79 MG	155 HC	P<0.05, OR=3.73
19793653	Pal Z (95)	*ORα*	rs2234693 rs9340799	Caucasian women	113 female myasthenia patients	184 female HC	P>0.05
18037500	Sakthivel P (96)	*PDCD1*	rs7565639	Sweden	269 MG	275	Significant increase in GG genotype among MG patients (age >40) compared to controls (p=0.0312).
24719132	Na SJ (97)	*SLAMF1*	rs3753381	Korean	55 AChR antibody positive MG	150HC	P=9.6391$\times 10^{-6}$
22617007	Kokunai Y (98)	*SCN4A*	G1292D	Swedish Caucasian	1 acquired autoimmune myasthenia gravis	547 HC	P<0.05
26632886	Nel M (99)	*TGFB1*	-387C>T	African	OP-MG	1000	
24959269	Zheng K (100)	*TIM1*	-1637A/G	Chinese	58 MG(+) thymoma	62	Thymoma (MG+) *vs.* Thymoma (MG+), P=0.031
4063586	Zheng, K. (101)	*TIM1*	-1637A/G	Han population of North China	58 cases of thymoma with MG, including 28 males and 30 females (mean age, 47.3 years)	62 cases of thymoma without MG, including 38 males and 24 females (mean age, 52.7 years)	The allele frequencies at the -1637A/G polymorphic site were significantly different between thymoma patients with and without MG (P=0.024)
25663933	Xu G (102)	*TIM3*	GT+TT genotype and T allele on the -574 locus	Han population of North China	116 patients with thymoma and MG	124 patients with thymoma, but without MG	GT+TT: 0.329 (0.171–0.634) T: 0.375 (0.202–0.697)
16075747	Guan YZ (103)	*TNF*	-308A/A	Chinese	20 MG	20	Significant increase in LOMG patients (age >40) compared to controls (P<0.05)
10376950	Huang DR (104)	*TNF*	TNF-α -308 allele 2	Swedish caucasian	19 MG patients, Serum AChR-Ab(-)=13.8% Serum AChR-Ab(+)=86.2% Thymoma=17.2% Hyperplasia=39.7% Normal=12.9% UnTx=30.2%	100 ethnically matched healthy individuls	–
28514294	Yang, Hong-Wei (105)	*TNFARP3*	rs7749323	47	47 LOMG	235	OR=3.27, 95% CI, 1.01–10.6, P=0.04
9949945	Zelano G (106)	*TNFB*	TNFB*1	Italy	63 MG patients (Hyperplasia =26; thymoma =17; involuted thymus =6; Not thymectomized =14) Forty-nine patients had been thymec-tomized: 26 had a thymic hyperplasia, 17 a thymoma and six a normal/involuted thymus.	93 healthy individuals	MG patients with thymic hyperplasia we found a positive association with the TNFB*1 allele [Relative risk (RR): 2.6; P<0.001] and phenotype (RR: 1.8; P<0.005) and a negative association with the TNFB*2/2 genotype (RR: 0.2; P<0.001) MG patients with thymoma we found a positive association with the TNFB*2/2 genotype (RR: 5.6; P<0.01) and a negative association with the TNFB*1 allele (RR: 0.3;P<0.05) and *1/2 genotype (RR: 0.2; P<0.01).
9688335	Hjelmström P (107)	*TNFB*	TNFa2 TNFa11 TNFB*1 TNFB*2/TNFB*2	Swedish Caucasian	79 MG (51 females and 28 males)	155 unrelated healthy individuals	TNFa2 was positively associated in all MG patients OR= 2.92, 95% CI: 1.57–5.43, Pc<0.01 TNFa11 was found to be decreased in patients with an early onset of disease compared to patients with a later onset OR=0.27, 95% CI: 0.09–0.75, P-0.05, Pc=ns TNFB*1 was observed in patients with an early onset of disease compared to patients with a later onset OR =3.27, 95% CI: 1.19–9.02, Pc<0.05. The frequency of the TNFB*2/TNFB*2 genotype was decreased in patients with an early disease onset OR=0.31, 95% CI: 0.11–0.84, P<0.05
23253802	Han JL (108)	*VDR*	s757343	Chinese	302 MG	283	1.70 (1.07-3.41)

EOMG, early onset MG; OP-MG, ophthalmoplegic complication of MG; EOM, extraocular muscle; LOMG, late-onset; RA, rheumatoid arthritis; p_c, denotes Bonferroni corrected probability values; CI, confidence interval.

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Table S3 Reported differentially expressed mircoRNAs in PBMC or serum in between MG cases and healthy controls

PMID	Authors	MG subtype	miRNAs	PBMC or serum	Ethnic group or descent	Fold changes	P value
22835429	Lin Jiang (109)	MG	let-7a	PBMC	Chinese	–41.40	P<0.0001
22835429	Lin Jiang (109)		let-7b	PBMC	Chinese	–28.90	P<0.0001
22835429	Lin Jiang (109)		let-7c	PBMC	Chinese	–52.20	P<0.0001
22835429	Lin Jiang (109)		let-7d	PBMC	Chinese	–33.50	P<0.0001
24962817	Zhangq J (110)	AChR-MG	miR-146a	PBMC	Chinese	4.00	P<0.0100
24036458	Lu J (111)	AChR-MG	miR-146a	B cell	Chinese	3.5	P<0.0100
24043548	Wang J (112)	EAMG	miR-145	PBMC	Chinese	–0.28	0.0130
24387321	Wang (113)	EAMG	miR-155	PBMC	Chinese	8.00	P<0.0010
24637658	Gisela Nogales-Gadea (114)	EOMG	miR-15b	Serum	Turkey	–37.13	P<0.0230
24637658	Gisela Nogales-Gadea (114)	LOMG	miR-122	Serum	Turkey	–311.05	P<0.0010
24637658	Gisela Nogales-Gadea (114)	LOMG	miR-140-3p	Serum	Turkey	–60.60	P<0.0040
24637658	Gisela Nogales-Gadea (114)	LOMG	miR-185	Serum	Turkey	–32.45	0.0020
24637658	Gisela Nogales-Gadea (114)	EOMG	miR-192	Serum	Turkey	–57.62	0.0200
24637658	Gisela Nogales-Gadea (114)	EOMG	miR-20b	Serum	Turkey	–4.48	0.0330
24637658	Gisela Nogales-Gadea (114)	LOMG	miR-885-5p	Serum	Turkey	–148.66	0.0140
23196978	Zhuoan Cheng (115)	MG	miR-320a	Serum	Chinese	–7.1428	0.0433
25356381	Tanel punga (116)	AChR-MG	miR-150-5p	Serum	Swedish	13.2	0.002
			miR-21-5p			3.3	0.011
			miR-27a-3p			–5.8	0.044
3992033	Wang (117)	MG	MiR-155	PBMCs	Chinese	5.8	P<0.05
26845056	Nie Chunjie (118)	MG	miR-20b	Serum	Chinese	0.6	P<0.05
25962782	Yong Zhang (119)	Ocular	miR-181c	PBMCs	Chinese	0.25	P<0.01
		generalized				0.45	P<0.01
26943954	Tanel Punga (120)	MuSK+ MG	miR-151a-3p	Serum	Roman	2.63	0.000887
			let-7f-5p			3.76	0.01040
			miR-423-5p			4.30	0.0118
			let-7d-3p			3.68	0.0178
			let-7a-5p			2.03	0.0327
			miR-409-3p			4.46	0.0351
26095457	Punga AR (121)	MG	miR-150-5p	Serum	Swedish	2.7	P<0.0001
			miR-21-5p			1.94	P<0.0001

Fold changes: miRNA expressions of MG patients *vs.* normal controls; EAMG, experimental autoimmune; LOMG, late onset MG; PBMC, peripheral blood mononuclear cell.

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