Functional annotation of Myasthenia Gravis genetic risk variants: results from a genome-wide study

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Abstract

Myasthenia Gravis (MG) is an autoimmune disease of the neuromuscular junction. The purpose of this study was to analyze the biological pathways and key genetic contributors that lead to MG. In this study, we performed functional annotation of the significant variants from the results of an MG Genome-Wide Association (GWAS) study on a Southeastern European population. Furthermore, the three approaches used were positional mapping of the SNPs, pathway analysis, and eQTL mapping. The positional and eQTL mapping were performed through FUMA. We annotated the SNPs to genes based on their physical position, and for the eQTL we used data from public repositories to test whether the expression of the gene is associated with allelic variation at the SNP. For the pathway analysis we used MAGMA; first, gene-analysis was performed in order to determine the p-value per gene based on whether the SNPs included in a gene were significantly associated with MG. Thirty-five genes were detected by all three approaches using the early-onset MG cases; all of them are located in the Major Histocompatibility Complex (MHC) region, which is reported to be associated with MG in previous studies. Five genes in the dataset including both early and late onset cases were detected by all three approaches, one being THEMIS and the other four are located in the MHC region. Overall, our study supports the results of previous studies as well as identifying novel risk factors. Further studies into the functions and mechanisms of these novel genes may allow researchers to develop therapeutics and treatments which would delay the progression of the disease or lessen the symptoms.

Introduction

Myasthenia Gravis (MG) is an autoimmune disease of the neuromuscular junction. It is a rare disorder which causes muscle weakness and fatigue, and the typical treatment currently is anticholinesterase drugs, immunosuppressive drugs or surgery. One of the characteristics of MG is the early (< 50 years old) vs late (≥ 50 years old) onset. The onset is found to have been sex-specific, with early-onset patients usually being females and late-onset patients usually being males (Gilhus, 2016). The purpose of this study was to analyze the biological pathways and key genetic contributors that lead to MG. In this study, we performed functional annotation of the significant variants from the results of an MG Genome-Wide Association (GWAS) study on a Southeastern European population. Furthermore, the three approaches used were positional mapping of the SNPs, pathway analysis, and eQTL mapping. From all three methods, we were able to detect five genes that were significantly associated with MG in the dataset including both early and late onset cases and 35 genes were detected from the early-onset dataset.

Materials

- Summary statistics data from in-house Myasthenia Gravis data set
- 43 MSigDB gene sets related to mechanisms in the development of MG and autoimmune disorders
- eQTL data from Blood eQTL Browser, BIOS QTL Browser (information from blood samples), and from GTEx data from samples of
  - o EBV-transformed lymphocytes
  - o whole blood
  - o skeletal muscle
  - o tibial nerve
  - o thyroid
- Chromatin interaction data from neural progenitor cells
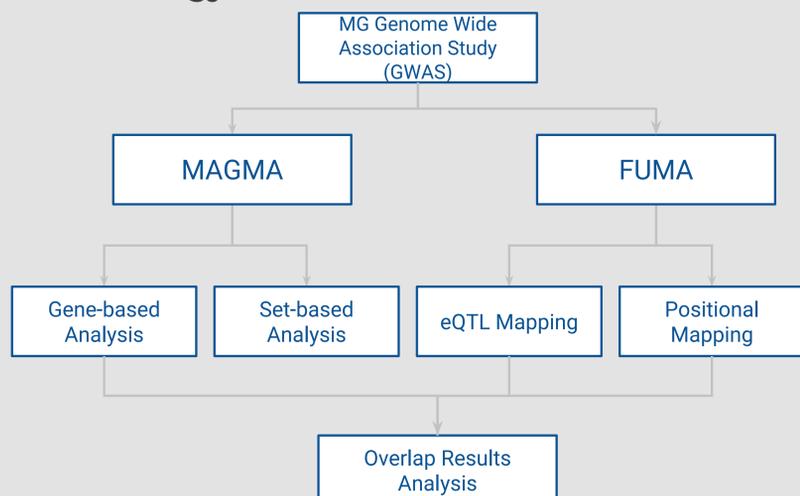
Methodology
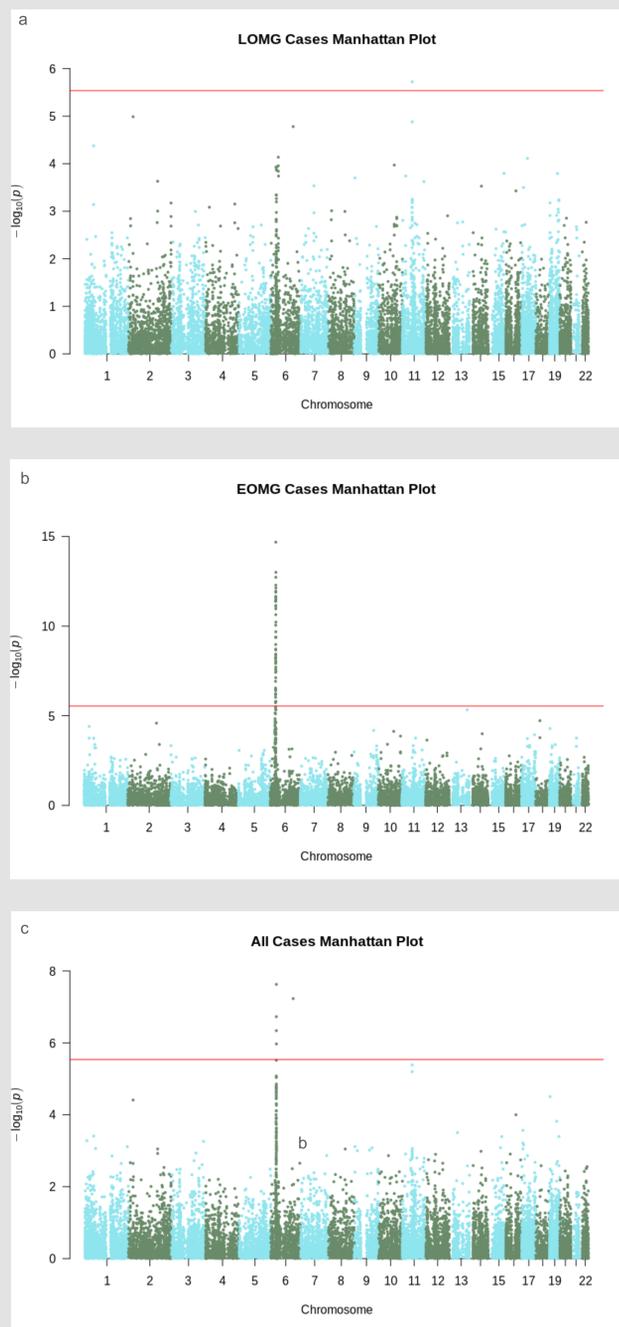

Figure 1: Schematic of Overall Research Approach

Results

Figure 2: Manhattan plots of MAGMA results

Genes Found in All 3 Methods:
N/A

Genes Found in All 3 Methods: APOM, ATF6B, ATP6V1G2, BAG6, C2, C6orf48, CDSN, CFB, CLIC1, CSNK2B, DDR1, DDX39B, GNL1, GTF2H4, HLA-B, HLA-DQA1, HLA-DRA, MICA, MICB, MSH5, NCR3, NOTCH4, PPP1R18, PRRC2A, PSORS1C1, SFTA2, SLC44A4, STK19, TCF19, TNXB, TRIM10, TRIM15, TRIM26, TRIM31, VARS2

Genes Found in All 3 Methods:
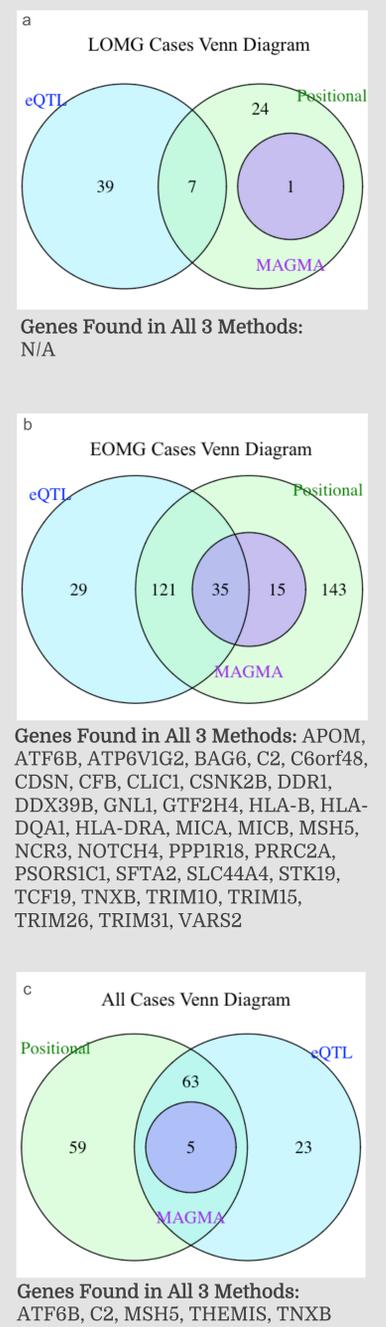ATF6B, C2, MSH5, THEMIS, TNXB

Figure 3: Venn Diagrams of overlapping results between eQTL mapping, positional mapping, and MAGMA methods

Conclusions

In performing this study, we aimed to find significant genes and pathways which are associated with Myasthenia Gravis. To summarize, our major findings are the 36 genes that were found in the results of positional mapping, eQTL mapping, and MAGMA from the early-onset and joint MG dataset; 35 were from the early-onset dataset and one unique gene was from the joint dataset. Additionally, the BioCarta Complement Pathway was found using MAGMA gene set-based analysis on the early-onset data. It is likely that these genes and pathways play some role in the development or progression of Myasthenia Gravis. In the next steps, we will perform a meta-analysis to determine whether our results overlap with previous MG studies and, if possible, to detect novel variants. Using these results we can progress our understanding of the disease. More specifically, further research into the THEMIS gene may prove useful as it is not located in the MHC region. Additionally, outside studies into the functions and mechanisms of the genes from our results may allow researchers to develop therapeutics and treatments which would delay the progression of the disease or lessen the symptoms.

References

de Leeuw C, Mooij J, Heskes T, Posthuma D (2015): MAGMA: Generalized gene-set analysis of GWAS data. PLoS Comput Biol 11(4): e1004219. doi:10.1371/journal.pcbi.1004219

Gilhus, N. E., M.D. (2016). Myasthenia Gravis. New England Journal of Medicine,375(26), 2570-2581. doi:10.1056/nejmra1602678

K. Watanabe, E. Taskesen, A. van Bochoven and D. Posthuma. Functional mapping and annotation of genetic associations with FUMA. Nat. Commun. 8:1826. (2017). https://www.nature.com/articles/s41467-017-01261-5

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