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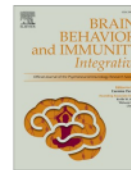
Integration of genomics database and bioinformatics to identify genome-wide variants for myasthenia gravis across multiple continents

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ABSTRACT

Autoimmune disease is an immune response that damages the body's tissues, thereby disrupting the body's physiological functions. Myasthenia gravis represents one such condition characterized by muscle weakness due to impaired neuromuscular transmission. While it can affect anyone, it tends to be more prevalent among women aged 20–30 and men over 50. This disease, deemed a genetic disorder, typically emerges in old age when antibodies target receptors in the muscles. In this study, we sought to identify the genes that can affect myasthenia gravis by leveraging several databases, including the GWAS Catalog, HaploReg, GTEx portal, and Ensembl. Specifically, our focus was on exploring genomic variants and the expression of the *LTA* and *CTLA4* genes. Our findings reveal that two variants (rs2071591 and rs231770) impact *LTA* expression in both muscle and brain tissue, while affecting *CTLA4* expression in testicular cell tissue. Subsequently, we assessed the allele frequency of these variants across regional populations, namely African, American, East Asian, European, and Southeast Asian. This study demonstrates that the *LTA* and *CTLA4* genes have a higher frequency in African, East Asian, and European populations compared to American and Southeast Asian populations. Consequently, our finding suggests that the latter two populations might have relatively higher susceptibility to the autoimmune disease myasthenia gravis. Therefore, variations in these genes not only offer insights into disease susceptibility, diagnostic or prognostic biomarkers, but also open up avenues for identifying candidate drug targets through genomic-driven drug repurposing.

1. Introduction

Myasthenia gravis (MG) is a neuromuscular disease characterized by voluntary muscle weakness (Sanders et al., 2017; Gilhus and Verschuuren, 2015). This disease has different symptoms that vary in other patients depending on the degree of involvement of the striated muscles. The most common symptoms in patients with myasthenia gravis are ocular symptoms, which present as ptosis and diplopia. These symptoms usually occur later in the day, and following activities such as watching TV or driving are more common. Excessive fatigue has been reported due to frequent exertion in patients with this disease. MG is an autoimmune disease that connects nerves to muscles (Murai, 2014),

produced by different antibodies against synaptic membrane proteins (Benatar et al., 2016). It usually accounts for more than 85% of cases and is caused by a type of antibody to the skeletal muscle acetylcholine receptor (AChR-Ab) (Berrih-Aknin et al., 2014). However, components other than AChR, such as muscle-specific receptor tyrosine kinase or lipoprotein-associated protein 4 (LRP4), can also be targeted for autoimmune attacks (Mehling et al., 2011).

Based on the mechanism of autoimmune disease and antibodies, molecular skeletal muscle invasiveness, thymus status, genetic characteristics, disease phenotype, and response to treatment, MG is divided into early and late ocular subtypes, seronegative, thymoma, LRP4. Diagnosis of the MG subtype influences treatment decisions and disease

prognosis (Kerty et al., 2014). Approximately 50% of patients with ocular MG develop generalized myasthenia gravis (GMG) over a 2-year, which affects other muscles and is manifested by visual weakness and symptoms (Khan and Wang, 2020).

According to a systematic population-based study, (Carr et al., 2010) estimated the incidence and prevalence of MG to be 54 per million and 77.7 per million, respectively. However, significant changes have been reported in various studies. The incidence of this disease has been shown to range between 1.77 and 21.3 per million people and a prevalence of 15 to 179 million people (Carr et al., 2010). Many epidemiological studies, especially in Western Europe and Asia, report significant differences in the incidence and prevalence of MG. The incidence of MG ranges from 1.7 to 30 per million per year (Breiner et al., 2016). This disease has two age peaks: 40–40 years, mainly affecting women, and the other: 80–60 years, which occurs equally in men and women (Benatar et al., 2016).

In summary, MG is a neuromuscular disorder characterized by muscle weakness, with its manifestations varying among patients. Ocular symptoms, notably ptosis and diplopia, are common, often exacerbated by activities like watching TV or driving. MG results from autoimmune processes triggered by antibodies against synaptic membrane proteins, predominantly the acetylcholine receptor (AChR-Ab). The disease is categorized into subtypes, impacting treatment choices and prognosis. Epidemiologically, MG's incidence and prevalence vary across regions and age groups. Genetic variations play a significant role, with GWAS cataloging relevant variants. This study aims to investigate the variants associated with MG through an approach based on bioinformatics, offering insights into disease susceptibility and progression. In addition, gene expression profile patterns and allele frequencies of genetic variant populations were assessed using various databases. The results will enable future studies to determine whether these variants may be associated with multiple risks of MG infection, as well as MG progression and disease susceptibility.

2. Method

This study employed a bioinformatics-based approach to prioritize pathogenic variants potentially linked to MG. A detailed outline of the study design is visually represented in Fig. 1. To collect data on MG-associated variants, we leveraged the GWAS Catalog from the National Human Genome Research Institute (NHGRI) Database (http://www.ebi.ac.uk/gwas), accessed on May 22, 2023. Employing the keyword "Myasthenia Gravis" (MG), we extracted information on variants associated with MG. We found a total 36 single nucleotide polymorphisms (SNPs) number of MG-associated variants. Next, subsequent analysis of MG-related SNPs was conducted using HaploReg (version 4.2) HaploReg is a tool designed to analyze non-coding genome annotations from published GWAS or new variants. It aids in understanding the functional outcomes of GWAS results, predicting potential causal variants, identifying involved cell types, and predicting candidate target genes (Ward and Kellis, 2016, 2012). In this study, the GWAS catalog inclusion criteria for SNPs were those with a *p*-value $< 10^{-8}$ (Lee et al., 2007). The investigation further entailed assessing associations between various genetic variants and gene expression profiles utilizing expression quantitative trait loci (eQTL) available on the GTEx Portal database (http://www.gtexportal.org/home/) (Blauwendraat, 2022) accessed on May 22, 2023. Then, we confirmed the variant using the Ensembl Genome Browser (https://www.ensembl.org/index.html) (Ozaki et al., 2004) accessed on May 22, 2023. In addition, allele frequencies of the MG-associated variants were evaluated across diverse populations, encompassing African, American, East Asian, European, and Southeast Asian people.
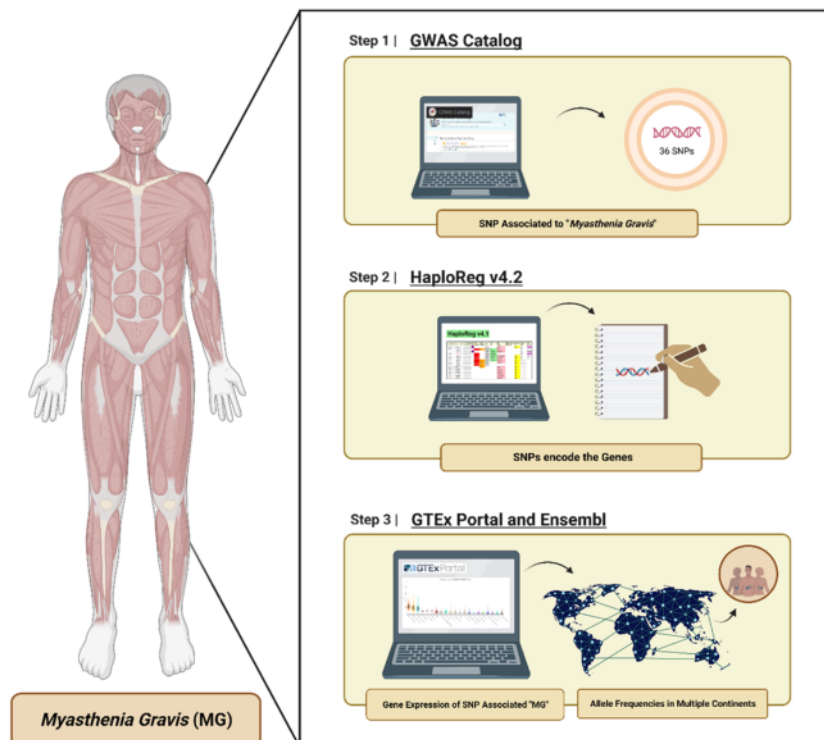

Fig. 1. Bioinformatics workflow for the identification of genetic variations associated with Myasthenia Gravis (MG).

3. Results

This study utilized the GWAS database to identify SNPs associated with MG. From the GWAS database, 36 SNPs associated with MG were identified with 26 unique SNPs associated with MG further identified after removing all SNP duplications (Table 1). Based on the number of SNPs obtained, the SNPs were forwarded using HaploReg version 4.2, with a p-value $< 10^{-8}$.

Based on the data presented in Table 2, this study focused on two genomic variants of the same gene that qualified as biological risk SNPs in this MG study. Using an integrative bioinformatics approach, two variants rs2071591 and rs231770 respectively encoding the *LTA* and *CTLA4* genes were prioritized as MG biological risk SNPs. Although these two variants does not show dbSNP functional annotation with missense mutation, however, by using HaploReg version 4.2 we identified the variant of rs2071591 near with rs1041981 variants which has missense mutation based on the criterion $r^2 > 0.8$. While for the variant with rs231770 near with the variant rs231775 which has missense mutation. MG disease is characterized by muscle and tissue weakness that occurs when the immune system is impaired and produces antibodies that attack the tissues in the body (Benatar et al., 2016). It was also reported that Lymphotoxin α (*LTA*) is a cytokine secreted by lymphocytes and is a member of the Tumor Necrosis Factor (*TNF*) family. *LTA* gene variations can contribute to threshold brain excitability, the spread of neural hyperexcitability (Aurora and Welch, 2000).

In Renton's et al. (2015), the gene for cytotoxic T lymphocyte-associated protein (*CTLA4*) was previously suggested as a cause of MG susceptibility. The *CTLA4* gene also multiplies when symptoms are present regardless of age, indicating that it is responsible for aberrant autoimmune responses that lead to neuromuscular junction dysfunction. *CTLA4* 45-kD immunoglobulin is expressed by activated T cells and has a significant sequence identity with CD28 (Renton et al., 2015).

3.1. LTA gene expression in muscle and brain tissues

In atherosclerotic plaques, intimal cells, some spindle-shaped or have globular, vacuolated cytoplasm, show immunoreactivity for *LTA* and

Table 1
GWAS catalog results are obtained from 26 SNPs with significance (p-value $<10^{-8}$).

SNP	p-value
rs3093958	4×10^{-42}
rs9271375	2×10^{-19}
rs4369774	6×10^{-19}
rs111945767	3×10^{-17}
rs76815088	6×10^{-16}
rs4409785	2×10^{-07}
rs4574025	7×10^{-14}
rs35274388	1×10^{-12}
rs2476601	2×10^{-12}
rs2071591	4×10^{-12}
rs150881176	1×10^{-11}
rs231770	9×10^{-11}
rs4574025	4×10^{-07}
rs9963862	4×10^{-07}
rs12653117	5×10^{-07}
rs6914704	2×10^{-06}
rs4128527	4×10^{-06}
rs4518467	4×10^{-06}
rs2476601	7×10^{-06}
rs9266277	7×10^{-10}
rs6998967	9×10^{-10}
rs35274388	1×10^{-09}
rs4263037	1×10^{-08}
rs73007767	4×10^{-08}
rs2245569	6×10^{-08}
rs9270986	6×10^{-08}

Table 2
The variant risk allele which codes two genes

SNP	GENCODE	p-value
rs2071591	*LTA*	4×10^{-12}
rs231770	*CTLA4*	9×10^{-11}

galectin-2. Binds to adjacent portions of anti-tender muscle (SMC) cells. Galectin-2 and *LTA* are expressed in human smooth muscle cells and macrophages affected by atherosclerotic lesions (Vergoossen et al., 2021).

In Feroni's (2022), states that *LTA* genes encode cytokines that can modulate many inflammatory, immunological, and antiviral responses. It has been postulated that the inflammatory process modulated by *LTA* may contribute to the propagation of neural hyperexcitability by acting as an initiation and maintenance factor during migraine attacks (Ma'ruf et al., 2023). These results agree with a study on 439 Korean migraine patients genotyped for several *LTA* gene polymorphisms (Lee et al., 2007). Migraines occur because the blood vessels in the brain experience dilation or expansion, the main form of headache, characterized by debilitating headache attacks and symptoms of autonomic nervous system dysfunction (Olesen, 2018) (Fig. 2).

3.2. Expression of the CTLA4 gene in the testis

Our new analysis does not show the *CTLA4* location in the previous GWAS (rs231770). After tracing using HaploReg version 4.2, it was found that the SNP rs231770 near with the variant rs231775 which is missense mutation according to the criterion $r^2 >= 0.8$, the SNP may show variations in alleles that impact the risk of MG in various populations. Although these loci still make biological sense, more extensive studies are needed to prove that they are related to each other (Blauwendraat, 2022).

Another study in Vergoossen 2021 said that almost all MG-related genes were found in the testes and ectocervix. This study did not say a specific *CTLA4* gene existed in testicular tissue. Still, the genes in question were *RAPSN* and *CHRNA1* expression mostly limited to skeletal muscle, with some additional words in the tibial nerve and the testicular and pituitary glands, respectively (Yasumizu et al., 2022). Overall, the expression of MG-related genes is prominent in skeletal muscle and brain, but individual genes are also expressed in other tissues of the human body (Vergoossen et al., 2021) (Fig. 3).

3.3. Relationship between LTA and CTLA4 genes with eQTL from the GTEx portal database

The GTEx Portal database aims to evaluate MG gene expression in various human tissues, including muscle tissue. Using the GWAS catalog database we found 26 SNPs with the highest p-values from this analysis. Based on the P-value criterion, two statistically significant SNPs were found and prioritized. Based on an extended SNP count analysis using HaploReg version 4.2, we prioritized the two SNPs at risk for MG because the functional annotations of the SNPs were $<10^{-8}$.

According to (Yasumizu et al., 2022), the increase in *CHRNA1* expression tend to be lower when compared with other neuromuscular antigens such as *GABRA5* and *RYR3*. Although a moderate rise in *CHRNA1* expression seems sufficient to cause severe symptoms in MG, it is related to the availability of acetylcholine receptor antibodies and their crucial biological role. These findings provide valuable clues for understanding the pathogenesis of various autoimmune neurological diseases. The following Table 3 shows the results of genetic variation from MG.
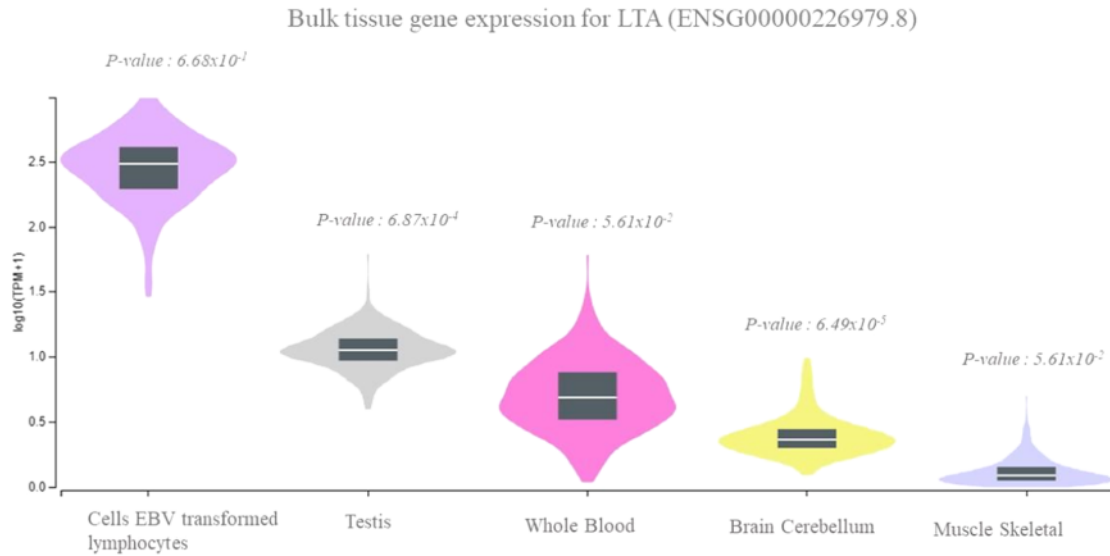
Bulk tissue gene expression for LTA (ENSG00000226979.8)

Fig. 2. *LTA* gene expression associated with myasthenia gravis across several human tissues from the GTEx Portal.

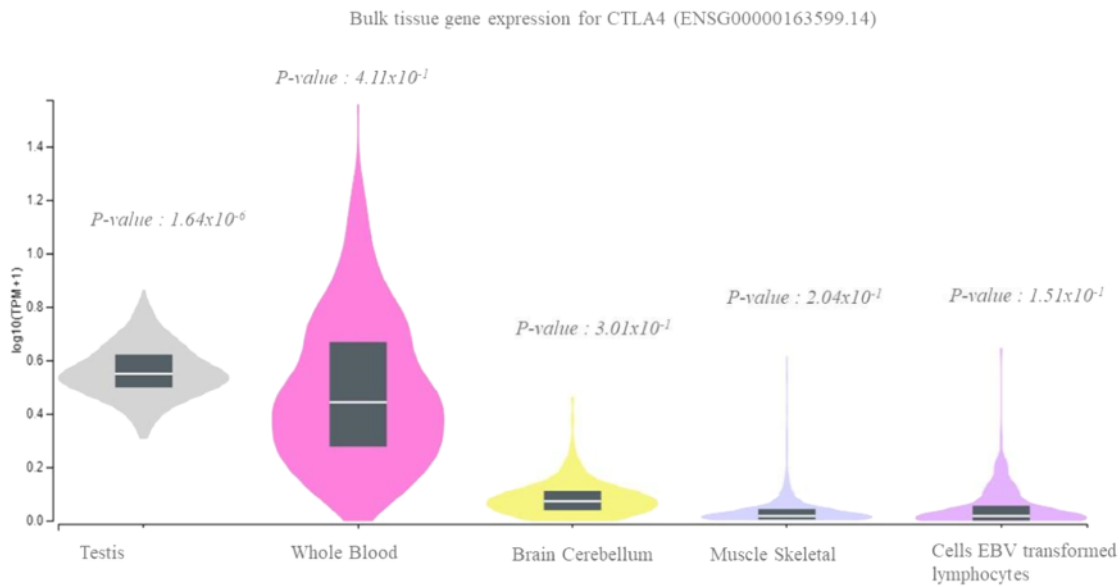Bulk tissue gene expression for CTLA4 (ENSG00000163599.14)

Fig. 3. CTLA4 gene expression associated with myasthenia gravis across several human tissues from the GTEx Portal.

Table 3
e-QTL's result for the Myasthenia gravis from GTEx portal database.

SNP	GENCODE ID (ENSG00000-)	Gene symbol	*p*-value	NES	Tissue	Actions
rs2071591	226979.8	*LTA*	0.000065	0.29	Brain - Cerebellum	GG>GA>AA
	226979.8	*LTA*	0.00024	0.14	Muscle - Skeletal	GG>GA>AA
rs231770	163599.14	*CTLA4*	0.0000016	-0.28	Testis	CC>CT>TT

3.4. Myasthenia gravis (MG) candidate variant allele frequencies across continents

After identifying candidate variants related to *LTA* and *CTLA4* gene expression, allele frequencies have been determined across populations of all continents, as shown in (Table 4). Allele frequencies for the two variants were evaluated in multiple continents, including populations of 1195 individuals (Africa), 567 individuals (America), 1112 individuals

Table 4
Allele frequencies for SNPs examined in this study.

SNP	Position (hg38)	Gene	p-value	Allele		Allele Frequency (N)				
				Ref	Eff*	AFR	AMR	EAS	EUR	SAS
rs2071591	Chr6 31548022	*LTA*	4×10^{-12}	G	A	0.512 (677)	0.336 (233)	0.469 (473)	0.310 (312)	0.261 (255)
rs231770	Chr2 203864430	*CTLA 4*	9×10^{-11}	C	T	0.392 (518)	0.481 (334)	0.634 (639)	0.379 (381)	0.306 (299)

(East Asia), 693 individuals (Europe), and 554 individuals (South East Asia). Using the Ensemble Genome Browser, we obtained allele frequencies in Africa, America, East Asia, Europe, and Southeast Asia (http://www.ensembl.org). Allele frequencies across populations differ for each *LTA* and *CTLA4* gene variant. Table 4 and Fig. 4. shows the gene expression level at a higher frequency of the related allele (T) rs231770 than the corresponding allele (A) rs2071591. In the associated alleles (T) rs231770 and (A) rs2071591, the African and East Asian populations are much higher than the American, Southeast Asian, and European Asian people.

The higher frequency of the related allele is (T) rs231770 compared to the other related allele, namely (A) rs2071591. In the associated alleles (T) rs231770 and (A) rs2071591, the African and East Asian populations are much higher than the American, Southeast Asian, and European Asian people. The rs2071591 allele indicated a differential variant prevalence contribution for *LTA* gene expression, while the rs231770 allele indicated a differential variant prevalence contribution for *CTLA4* gene expression.

Allele frequencies in all populations differ for each SNP, as shown in Fig. 4. It is generally known that the A and T allele frequencies for rs2071591 and rs231770 also appear to have a higher frequency in Europe with alleles rs2071591 (47%), rs231770 (63%), East Asia with alleles rs2071591 (47%), rs231770 (63%), compared to America with alleles rs2071591 (34%), rs231770 (48%), Africa with alleles rs2071591 (51%), rs231770 (39%), Asia southeast with alleles rs2071591 (26%), rs231770 (31%).

Identification of gene variations that are unique and pathogenic for a disease is very interesting for clinical research and validation. Identification of these variants not only provide clues to disease susceptibility or as a diagnostic and prognostic biomarker (Irham et al., 2022) but also can be used to discover candidate drug targets or what is known as drug repurposing (genomic-driven drug repurposing) (Irham et al., 2020; Afief et al., 2022). The authors hope that the discovery of the candidate gene variations can be validated in clinical settings and can become a diagnostic and prognostic biomarker for MG disease.

In conclusion, a bioinformatics-based approach revealed pathogenic variants potentially associated with MG. We propose that this variant may be used for further studies to identify MG and prognosis diagnostic biomarkers. However, we acknowledge that there are limitations to the bioinformatics-based approaches used to investigate genetic variants associated with MG. Notably, not all variants necessarily correspond to the identifiable gene (i.e., non-coding variants). Even when genes or genetic variants are present, they might not be suitable drug targets. Therefore, we recommend further clinical validation to corroborate our findings and gain deeper insight into the etiology and functional implications of MG disease.

4. Conclusion

In this study, we utilized a state-of-the-art bioinformatics approach
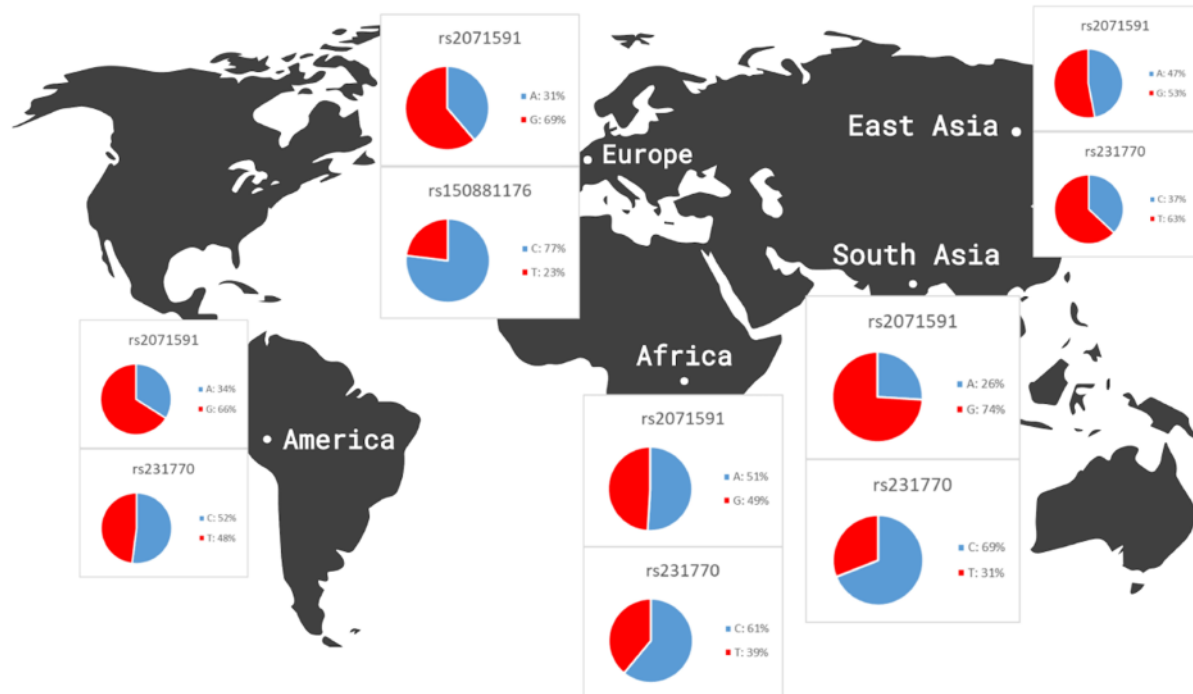

Fig. 4. Summary of allele frequency analysis of *LTA* and *CTLA4* gene expression in Africa, America, East Asia, Europe, and Southeast Asia.

to analyze genomic databases revealing distinct gene expressions of the *LTA* and *CTLA4* genes across muscle, brain, and testicular cell tissues for MG disease. Prominent gene variants include rs2071591, expressed in muscle and brain tissue, and rs231770, prevalent in testicular cell tissue. Notably, these variants exhibit an overall higher frequency in Europe with alleles rs2071591 (47%), rs231770 (63%), East Asia with alleles rs2071591 (47%), rs231770 (63%), in comparison to America with alleles rs2071591 (34%), rs231770 (48%), Africa with alleles rs2071591 (51%), rs231770 (39%), and Southeast Asia with alleles rs2071591 (26%), rs231770 (31%). We recommend that the discovered candidate gene variations be validated clinically, which could serve as diagnostic or prognostic biomarkers for MG.

Declaration of Competing Interest

The authors disclose no conflict of interest.

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