PNAS LETTER

Novel genes/loci validate the small effect size of ERBB2 in patients with myasthenia gravis

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Recently, Chia et al. performed a genome-wide association study (GWAS) involving 1,873 patients diagnosed with myasthenia gravis and 36,370 healthy individuals to identify disease-associated genetic risk loci (1). They detected that the *CHRNA1* and the previous association signals were confirmed. Then they employed a transcriptome-wide association study (TWAS) to test the effects of disease-associated polymorphisms on gene expression. *CHRNB1* and *ERBB2* were recognized as genes predicted to increase disease risk. We agree with their views on the function of *CHRNB1* and *ERBB2* in myasthenia gravis. Importantly, they indicated early- and late-onset cases have genetic differences. Apart from this, they also confirmed a genetic link between myasthenia gravis and other autoimmune diseases. Finally, Chia et al. identified potentially druggable genes/proteins and pathways. However, the authors did not investigate why *ERBB2* had a small effect size in colocalization analysis, which prompted us to conduct further statistical analysis (1).

Mendelian randomization (MR) utilizes genetic variation as the proxy for randomization to search for pleotropic/potentially causal effects of exposure on outcome. Different from conventional randomized controlled trials, MR minimizes confounding and reverses causation that is common in traditional association studies (2, 3) and has been applied to the identification of various phenotypes, such as COVID-19 (4), type 2 diabetes (5), and amyotrophic lateral sclerosis (6, 7) (Fig. 1*A*). Genetic variants were screened from two types of data: One GWAS of Chia et al. (1,873 myasthenia gravis patients and 36,370 healthy controls) (1) and the other expression quantitative trait loci (eQTL) data in normal skeletal muscle, peripheral nerve, and whole blood obtained from the public GTEx database (8). Using methods previously reported, the summary data-based MR (SMR) method and HEIDI test (heterogeneity in dependent instruments)

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The authors declare no competing interest.

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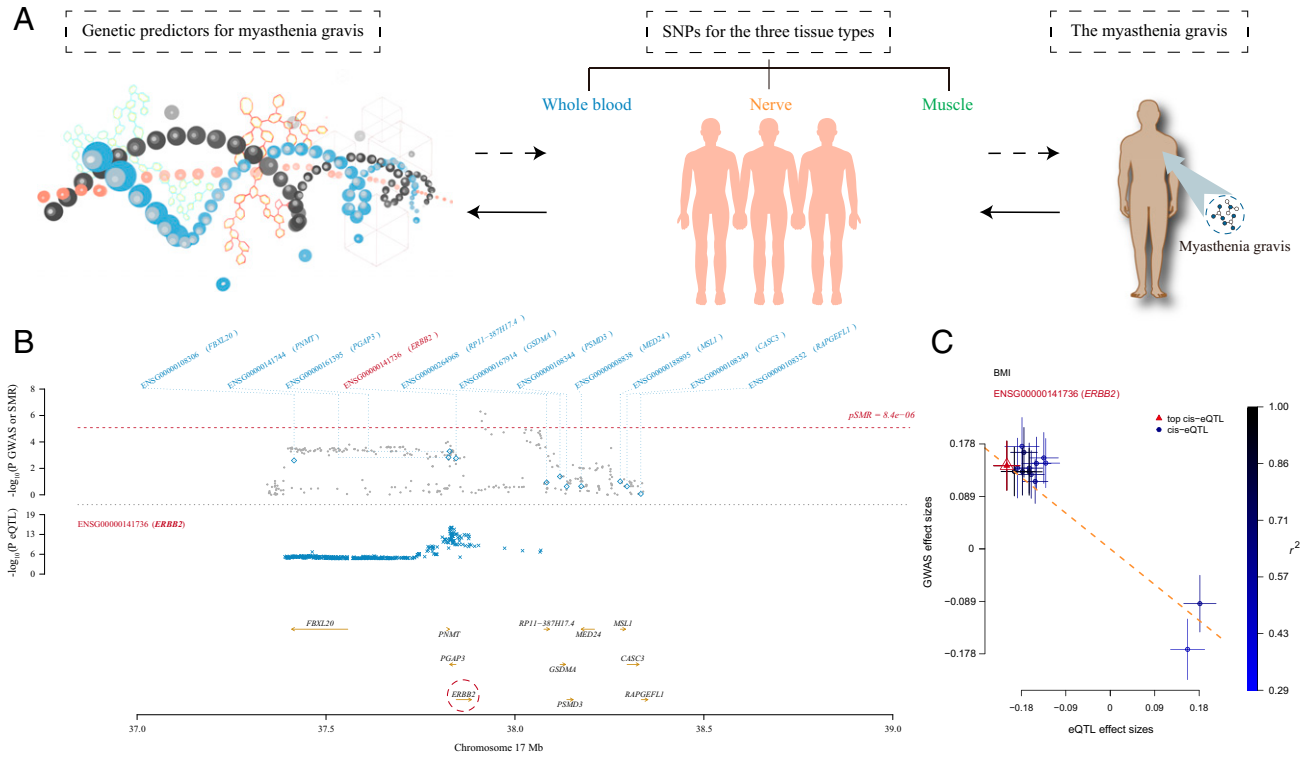

Fig. 1. Genomic genes identified by SMR. (*A*) Schematic diagram of the MR method. (*B*) SMR locus plot for ERBB2. (*C*) SMR effect plot for ERBB2.

Table 1. Genetic loci/genes verification of Chia et al. (1) for myasthenia gravis by SMR

Gene	Chromosome	ID	Tissue	P_{GWAS}	P_{eQTL}	$P_{SMR}(P_{Bonferroni})$	P_{HEIDI}
HLA-DRB5	6	rs9271055	Whole blood	5.69E-06	4.04E-127	8.07E-06(0.048)	0.036
HLA-DRB5	6	rs9271055	Muscle	5.69E-06	4.41E-305	6.50E-06(0.040)	0.035
HLA-DRB5	6	rs9271055	Nerve	5.69E-06	4.65E-104	8.75E-06(0.073)	0.029
ERBB2	17	rs1565922	Nerve	6.50E-04	1.38E-15	1.73E-03(1)	0.38
CHRNB1	17	rs4151121	Muscle	1.13E-05	5.21E-73	1.99E-05(0.12)	0.85

were applied to implicate loci in myasthenia gravis (9). The causal genes/loci that could be regarded must meet two standards: 1) significantly related to myasthenia gravis ($P_{SMR} < 0.05$) and 2) pass the heterogeneity test ($P_{HEIDI} > 0.05$). Based on the SMR analysis, altogether 61 novel genes/loci were identified across tissues, such as *HLA-DOB*, *MIF*, and *PNP* representing the prior genes ($P_{SMR} < 0.05$, $P_{HEIDI} > 0.05$). Additionally, we focused on TWAS implicating genes/loci in the Chia et al. study (1). *HLA-DRB5* was significantly associated with myasthenia gravis risk across tissues, with a high degree of consistency with Chia et al. (1). Crucially, *CHRNB1* and *ERBB2* were significant in muscles and nerves, respectively ($P_{SMR} < 0.05$; Table 1). Particularly, *CHRNB1* may be a causal gene for myasthenia gravis rather than a linkage or pleiotropic effect ($P_{SMR} = 1.99E\text{-}05$, $P_{HEDI} = 0.85$; Table 1) (10). Consistent with Chia et al. (1), *ERBB2* maintains a low heterogeneity test value ($P_{HEDI} = 0.38$) but may still be a critical genetic locus for myasthenia gravis ($P_{SMR} = 1.73E\text{-}03$; Fig. 1 *B* and *C*).

Overall, our SMR results identify genes/loci and provide insights into the role of *ERBB2*, suggesting a critical role in the myasthenia gravis pathogenesis mechanism. Simultaneously, this method replicates the loci/genes identified by Chia et al. (1), providing compelling evidence for the robustness of their study.

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