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Content

IDENTIFICATION OF POTENTALLY CAUSAL VARIANTS FOR MYASTHENIA GRAVIS: A BIOINFORMATICS-DRIVEN FINE-MAPPING APPROACH COMBINED WITH GENETIC ASSOCIATION STUDY

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Introduction: Genome-wide association studies (GWAS) identify genomic loci that contain genetic determinants of complex diseases. Subsequent functional genomic approaches, such as bioinformatic fine-mapping and transcriptome-wide association studies (TWAS), can reveal potentially causal single nucleotide variants (SNVs) that can be tested on patient samples. We applied this approach to study causal SNVs for acetylcholine receptor (AChR) seropositive myasthenia gravis (MG). We focused on *CHRNA1* and *CHRNB1* loci, coding AChR subunits, and *CTLA-4* locus, coding protein transmitting an inhibitory signal to T cells.

Methods: *CHRNA1* was fine-mapped by PAINTOR using data from GWAS summary statistics, 1000 genome and RegulomeDB. Alongside, rs4151121 identified by TWAS in *CHRNB1*, and *rs231735 and rs231770* identified by fine-mapping in *CTLA-4* were studied. SNVs were genotyped using allele discrimination assays in 447 Serbian AChR-MG patients (183 early-onset and 264 late-onset) and 447 sex- and age-matched controls.

Results: *CHRNA1* rs35274388 was fine-mapped as a potentially causal variant (PIP2=92%) exhibiting transcription factor binding and chromatin accessibility peaks. *CHRNA1* rs35274388 minor allele A and *CHRNAB1* rs4151121 minor allele G increased the risk for late-onset MG (OR=1.669, 95% CI=1.05-2.638, p=0.027, p10e^6 permutation=0.031 and OR=1.322, 95% CI=1.063-1.644, p10e^6 permutation=0.014, respectively). On the other hand, *CTLA-4* rs231735 recessive genotype TT decreased, while rs231735-rs231770 haplotype GC increased the susceptibility to early-onset MG (OR=0.548, 95% CI=0.339-0.888, p=0.014, p10e^6 permutation=0.014 and OR=1.360, p=0.027, p10e^6 permutation=0.027, respectively).

Conclusion: *CHRNA1* rs35274388 and *CHRNAB1* rs4151121 loci could be causal genetic factors for late-onset MG while *CTLA-4* rs231735 and rs231770 could be causal genetic factors for early-onset MG in Serbian population.

Key words: myasthenia gravis; GWAS; fine-mapping; *CTLA-4*; *CHRNA1/B1*

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