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Abstract

The therapeutic use of interferon (IFN) is known to cause depression that frequently interrupts treatment. Depression is a common (15–45%) side-effect of IFN-α treatment. To identify genetic variants associated with IFN-induced depression, we conducted a genome-wide association study (GWAS) of 224 Japanese chronic hepatitis C patients receiving IFN-based therapy in a multicenter prospective study and stratified them into two groups according to the Beck Depression Inventory, Second Edition (BDI-II) score. In the GWAS stage, we selected 42 candidate single nucleotide polymorphisms (SNPs) to perform replication analysis in an independent set of 160 subjects. The SNP rs1863918 in strong linkage disequilibrium with SNPs located around the Zinc finger 354C (*ZNF354C*) gene on chromosome 5 showed a significant association when the results of GWAS and replication were combined (odds ratio=2.55, P=7.89×10^{-8} in the allele frequency model), suggesting that the rs1863918 T allele was associated with IFN-induced depression. Furthermore, logistic regression analysis showed that rs1863918 T allele, a history of depression, and younger age were independent predictive factors for IFN-induced depression. Interestingly, western blotting and immunofluorescence showed that ZNF354C was highly expressed in the hippocampus in mice, a region implicated in the pathology of psychiatric symptoms. In conclusion, we identified rs1863918 as significantly associated with IFN-induced depression, and revealed that the candidate gene *ZNF354C* is highly expressed in the hippocampus of mice. Our data might be useful for elucidating the pathogenic mechanisms of depression induced by drugs including IFN.