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**Multomics Analyses Reveal Significant Association of SNP rs148582811 in ARVCF With Smoking Addiction by Affecting Nicotine-Associated Hippocampus-Dependent**

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**Backgrounds:** Although numerous susceptibility loci are nominated for nicotine dependence (ND), there was no report showing any association of ARVCF with ND or other addictions. The purpose of this study was to determine how ARVCF involves in the pathogenesis of ND.

**Methods and Results:** Through genome-wide sequencing analysis, we first identified genetic variants associated nominally with ND and then replicated them in an independent sample. Of the six replicated variants, rs148582811 in ARVCF locates in the peaks of enhancer-associated markers. The effective-median-based Mendelian randomization analysis indicates that ARVCF is a causal gene for ND. RNA-seq analysis detected decreased ARVCF expression in smokers relative to nonsmokers. Luciferase reporter assays indicate that rs148582811 and its located DNA fragment regulate ARVCF expression in an allele-specific way. Immunoprecipitation analysis revealed that transcription factor X-ray repair cross-complementing protein 5 (XRCC5) is bound to the DNA fragment containing rs148582811 and allele-specifically regulates ARVCF expression at the mRNA and protein levels. Finally, with the *Arvcf* knockout mouse model, *Arvcf* deletion not only impairs hippocampus-dependent learning and memory, but also alleviates nicotine-induced memory deficits.

**Conclusion:** In summary, this study demonstrates for the first time that ARVCF is a novel causative gene for ND, which plays a key role in nicotine-associated hippocampus-dependent memory.