

## Genomewide association study identifies a novel locus for cannabis dependence

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Despite moderate heritability (50-60%), only one study has identified genomewide significant loci for cannabis-related phenotypes. We conducted meta-analyses of genomewide association study (GWAS) data on 2,232 DSM-IV cannabis dependent cases and 6,257 cannabis exposed controls of European descent. A cluster of correlated single nucleotide polymorphisms (SNPs) in a novel region on chromosome 10 were genomewide significant (lowest  $p = 1.33 \times 10^{-9}$ ). Among the SNPs, rs1409568 showed enrichment for H3K4me1 and H3K427ac marks, suggesting its role as an enhancer in addiction-relevant brain regions, such as the dorsolateral prefrontal cortex and the angular and cingulate gyri. This SNP is predicted to modify binding scores for several transcription factors. We found evidence for replication for rs1409568 in an independent cohort of African-American (896 cases and 1519 controls) but not European-American (781 cases and 978 controls) participants. There was also evidence that the minor allele was associated with a 2.6% increase in right hippocampal volume in an independent sample of 430 European-American college students (fwe- $p=.007$ ). The identification and characterization of genomewide significant loci for cannabis dependence is amongst the first steps towards understanding the biological contributions to the etiology of this psychiatric disorder which appears to be rising in some developed nations.

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