

## Risk alleles identified in a genome-wide gene-by-cannabis dependence interaction analysis of risky sexual behaviors

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We conducted a genome-wide gene-environment interaction analysis to identify genetic variants that interact with cannabis dependence (CaD) in influencing risky sexual behaviors (RSB) and increasing risk of sexually transmitted infections (STI) and human immunodeficiency virus (HIV). Our sample included 3,350 African-American (AA) and European-American (EA) subjects (CaD: 43%; AA: 56%; Women: 33%; STI+: 33%; HIV+: 6%). A DSM-IV CaD diagnosis and RSB were evaluated using the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA). RSBs were analyzed as a score that takes into account experiences of unprotected sex and multiple sexual partners. We identified a genome-wide significant locus in AAs (*S100A10* rs72993629,  $p=2.73 \times 10^{-8}$ ) and a potential trans-population signal in women (*CLTC* rs12944716,  $p=5.27 \times 10^{-8}$ ). *S100A10* rs72993629 also showed a trend in the interaction with CaD in determining both STI and HIV status ( $p=0.054$  and  $p=0.071$ , respectively). A gene-based analysis also identified *TMOD2*, a neuronal-specific tropomodulin, as a candidate in both ancestry groups (AA  $p=9.49 \times 10^{-3}$ ; EA  $p=6.10 \times 10^{-3}$ ). A resting fMRI follow-up analysis of *S100A10* rs72993629 conducted in an independent cohort showed two significant associations: reduced power of the left paracentral lobule in ALFF (Amplitude of Low Frequency Fluctuations) analysis ( $p=7.8 \times 10^{-3}$ ), and reduced power of right pallidum in fractional ALFF analysis ( $p=4.6 \times 10^{-3}$ ). The activity of these brain regions is known to be involved in sexual functions and behaviors. The *S100A10* result functionally recapitulated our previous *S100B* finding observed in a genome-wide association study of CaD. The probability of identifying two of the 19 known *S100* genes in two independent genome-wide investigations by chance is approximately one in 1,100,000. The *S100A10* and *S100B* genes, which are located on different chromosomes, encode highly specialized calcium binding proteins. These data strongly support a role for calcium homeostasis in cannabis use and behaviors that it may influence.