WHOLE GENOME SEQUENCE STUDY OF CANNABIS DEPENDENCE: ASSOCIATIONS WITH REGULATORY ELEMENTS IDENTIFIED BY THE ROADMAP EPIGENOMICS PROJECT

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Quantitative genetic studies suggest substantial genetic influences contribute to the development of cannabis use disorders. Nonetheless, linkage and association studies attempting to identify specific genomic regions or variants that contribute to the development of cannabis use disorders have had limited success. The present report utilized low-coverage whole genome sequencing (WGS) in two family-based sample enriched for alcohol and other drug use to identify regulatory elements that might harbor rare variants that influence risk for cannabis dependence. The first cohort included 697 participants of predominantly Native American ancestry recruited from 8 geographically contiguous reservations. The second cohort included 1832 predominantly European ancestry individuals recruited as part of the UCSF Family Alcoholism Study. Participants from both cohorts were assessed for the presence of cannabis dependence using the Semi-Structured Interview for the Genetics of Alcoholism (SSAGA). Data-analyses were conducted in each population using a linear mixed model approach with ancestry estimates for the four major continental populations included as covariates to account for potential inflation in the test statistics resulting from population and family structure. Set-based tests of rare variation using the sequence kernel association test (SKAT) were conducted for variants with a minor allele frequency < 0.02 and located within regulatory regions identified by the NIH Roadmap Epigenomics Project. Combining p-

values across cohorts yielded significant associations that survived correction for multiple testing with variants located in a regulatory region of the *MEF2B* gene on chromosome 19 and a regulatory region of the *PCCB* gene on chromosome 3. Both genes have been previously linked to psychiatric disorders with the latter showing significant associations with schizophrenia and addiction-related phenotypes. The implications of these results for future sequencing studies of substance use disorders will be discussed.