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Genetic variants influence DNA methylation on Cocaine Use in the Veterans Aging Study Cohort

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Background. Associations between DNA methylation (DNAm) and cocaine use arise from exposure to the drug and genetic variation, which has its effect on cocaine use by influencing DNAm (i.e., Methylation Quantitative Trait Loci (meQTLs)). To further understand mechanisms underlying cocaine-associated DNAm, we mapped cis-meQTLs (defined as within 1 mega base flanking window of CpG sites) for cocaine use in a Veterans Aging Cohort Study Biomarker Cohort (N=598) which mainly consisting of samples with African ancestry (81%).

Rationale. Shu *et al.* recently reported significant differential DNAm associated with persistent cocaine use. Identifying meQTLs is an important next step to better understand genetic and epigenetic effects associated with cocaine use.

Hypothesis. cis-meQTLs contribute to cocaine use-associated DNAm.

Results. We identified 823 index cis-meQTLs for 284 CpG sites associated with cocaine use. The 823 meQTLs were enriched on the pathways involving immunity, cell adhesion and calcium ion binding, and repressing transcription factor binding. Among the identified meQTLs, we further found 76 CpG sites where there was a significant interaction by which persistent cocaine use altered the SNP - DNAm associations. One representative example was that effect of rs115797785 on the CpG site cg22244940 (mapped to *MMP17*) would be amplified when cocaine was used persistently.

Discussion. Our results show both exposure and genetic variants drive differences in DNAm associated with cocaine use. While future studies to replicate these findings and comparisons with meQTLs in brain tissues are warranted, these results suggest that leveraging epigenetic associations can help identify novel genetic drivers of cocaine use.