Epigenome-wide association study of opioid dependence in European American women

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Opioid dependence (OD) is currently epidemic in the US. Although OD has a higher prevalence in men, fatal opioid overdoses have increased at a higher rate among women. Epigenetic mechanisms have been implicated in the increased risk for OD, however, most studies to date have used candidate gene approaches, mainly focusing on the opioid receptor mu 1 (*OPRM1*) gene. In this study, we conducted the first epigenome-wide association study (EWAS) of OD in women. DNA was derived from whole blood samples and EWAS was assessed using the Illumina Infinium HumanMethylationEPIC array. Our sample included 111 European American women who were administered the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA), which yields a DSM-IV diagnosis of OD. To identify differentially methylated CpG sites, we performed an association analysis using the 'cpg.assoc' function from the minfi Bioconductor R package, adjusting for age, estimates of cell proportions, and the first 3 principal components estimated using the Barfield et al. method to correct for population stratification. Association analysis identified a significant differentially methylated CpG at cg19642402 (p= 4.6 x 10^{-8}, FDR = 0.03) located within the proline-serine-threonine phosphatase interacting protein 1 (*PSTPIP1*) gene. *PSTPIP1* is involved in inflammatory responses. When the top 10 ranked differentially methylated CpGs were used in a gene-based functional enrichment analysis, "response to stress" emerged as the top significant GO biological process (p = 7.35 x $10^{-6,}$FDR = 0.005). If replicated, our results would suggest that changes in DNA methylation at *PSTPIP1* may play a role in OD in women and implicates stress response as a potential mechanism of that effect. Two limitations of this study are the modest sample size and the use of blood for DNA extraction given the tissue-specific DNA methylation changes.