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Identifying novel genes and pathways associated with opioid overdose death via meta-analysis of differential gene expression.

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Only Recently have human postmortem brain studies of differential gene expression (DGE) associated with opioid overdose death (OOD) been publisher: Corradin et al. 2022; Mendez et al. 2021; Seney et al. 2021; Sosnowski et al. 2022. The four independent studies had modest samples sizes (N=40-153 decedents). We conducted a transcriptome-wide meta-analysis to increase statistical power and better understand the neurogenetics of opioid addiction. All studies had RNAseq data from human prefrontal cortex. For the meta-analysis we passed these data through consistent processing, QC, and modeling, then used a weighted Fisher's test (N=285 independent decedents; 20,098 genes) to identify OOD-associated DGE. The results identified 335 genes with significant DGE (FDR $p<0.05$). Of the 314 genes reported in prior DGE studies, 66 were retained as significant in this meta-analysis, including known genes/gene families (e.g., *OPRK1, NPAS4, DUSP, EGR*). The remaining 269 significant genes were novel (e.g., *NR4A2, SYT1, HCRTR2*). Enrichment analyses of all three gene sets (335 complete meta-analysis genes, 66 known genes, and 269 novel genes) showed significant enrichment for the Orexin receptor pathway (Bonferroni p=8.39e-4). Novel genes strengthened enrichment for the Orexin pathway, GO biological processes, and associated diseases, beyond the 66 previously reported genes. These associations suggest broad gene dysregulation in the prefrontal cortex and highlights the Orexin receptor pathway as a key finding in humans, addiction, including evidence of the Orexin system as a promising target for opioid addiction treatment development.