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The First GWAS of Opioid Overdose Death Yields Surprisingly Strong Associations and Trans-Ancestral Agreement

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We conducted the first genome-wide association study of opioid overdose death (OOD). Our sample included decedents of European ancestry (EA) or African ancestry (AA) ascertained via Medical Examiners' (ME) cause of death. Phenotypic data were obtained from ME records including post-mortem toxicology results. DNA was extracted from dried blood samples. Comparison group data were obtained via dbGaP for population controls of similar ancestry. Analyses incorporated steps designed to minimize spurious associations. Comparing 8081 EA cases and 23,409 controls, we identified 8 genome-wide significant (GWS) signals. The strongest (OR 0.75; p=3.26 E-20) was observed for rs1799971, a non-synonymous *OPRM1* SNP; our signal was markedly more significant than those in opioid use disorder (OUD) meta-analyses, likely indicative of additional liability for OOD. SNP heritability was estimated to be 16.6% (SE .011). Genetic correlations were high for OUD (0.76), cannabis use disorder (0.79), and addiction risk factor (0.89). Correlations for PTSD (0.61), ADHD (0.59), chronic pain (0.48), and all-cause mortality (0.69) exceeded values reported for OUD. Comparing 5474 AA cases and 7725 controls, we identified 6 GWS signals, the strongest (1.21; p=1.88 E-12) being rs11651708, an intronic SNP in *PRKCA*. This gene encodes protein kinase C alpha which has well-demonstrated involvement in opioid-induced respiratory depression. Trans-ancestral meta-analysis found substantial strengthening of four EA signals (e.g., rs1799971 p=1.38 E-25) and seven additional GWS signals. Further examination noted significantly stronger association for rs1799971 in cases with no fentanyl present (for both EAs and AAs). Our findings highlight the benefits of examining severe, definitively-defined phenotypes in diverse samples.