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Genomic analyses of prescription opioid dose in chronic opioid exposure

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Background: The long-term use of high dose opioids is associated with increased risk of accidental overdose and high percentage of patients treated with them will develop opioid use disorder. The recent opioid epidemic in the US largely has its origin in the over-prescription of opioid analgesics to treat chronic pain. Individuals with more severe pain may require higher doses. Other patients may develop opioid tolerance or need higher doses to try to counteract opioid-induced hyperalgesia. Higher dose requirements may also reflect differential opioid metabolism. **Purpose:** Our goal was to evaluate the contribution of genetic variation to prescription opioid dose in individuals treated for chronic pain. **Method:** We performed GWAS of the final dose (daily morphine equivalents) of any opioid analgesic in patients in the DiscovEHR cohort who received at least three (≥30 days each) prescriptions of opioids in 9 months window. Imputed genotyped data from 3,845 individuals were used as the discovery set and additional 2,561 individuals were used as the replication set. **Results:** Genome-wide significant associations with opioid dose were observed in multiple loci including CYP2B6 and NMD3. CYP2B6 encode a P450 enzyme known to metabolize opioids and the NMD3 gene has previously been associated with Parkinson's disease. **Conclusion:** This supports the validity of analyzing the genetics of opioid dose using electronic health records and indicates that common SNPs contribute to chronic opioid dosing requirements. In the future these analyses may help us identify patients likely to require high dose opioids for long-term use.