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Rat reduced complexity model of oxycodone self-administration and stress responsiveness

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Opioid use disorder (OUD) is a devastating psychosocial disease strongly modulated by genetic and environmental factors, including stress. DNA variants that contribute to OUD are largely unknown. WMI and their nearly isogenic control WLI rat strains were selectively bred from Wistar Kyoto (WKY) stock. Stress-vulnerable WMI self-administer significantly higher levels of oral oxycodone (OXY) than WLI. Here we test the idea that genetic differences cause variation in stress reactivity and in OXY intake.

Both strains were sequenced using Illumina, IonTorrent, and 10X Chromium technologies (>100X coverage). Targeted resequencing was used to validate variants and design marker panels for mapping studies. We identified 4,296 high quality SNPs and indels, including high impact variants in stress response and psychiatric disease associated genes (*Gnat2*, *Prlr*, *Nlrp1a*, *Pou6f2*, *Kdm5a*, *Reep3*, *Wdfy3*, *Pigr*). We detected strong effects of strain on OXY operant self-administration across a range of doses (0.025–0.2 mg/ml)—for example at 0.1 mg/ml ($F_{2,22}=7.54$;$p<0.01$;$\omega p^2=0.32$) and at 0.2 mg/ml ($F_{2,22}=18.64$;$p<0.001$;$\omega p^2=0.56$). Intake was highest at 0.1 mg/ml and the WMI phenotype was recessive; highest intake in WMI (2.55±0.42;N=10) relative to both WLI (1.3±0.23;N=5) and F1 hybrids (1.10±0.18;N=13).

We have validated a very low degree of sequence differences between WMI and WLI, yet still demonstrated heritable differences in OXY intake likely to be caused by pre-existing differences in stress responses. The small number of variants makes these sister strains an ideal resource for reduced complexity cross mapping and for the rapid identification of DNA variants, genes, and pathways driving differences in stress and drug responses.