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BALB/c substrain differences in whole brain concentrations of the highly potent oxycodone metabolite, oxymorphone map to chromosomes 5, 10, and 16 in a reduced complexity cross.

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Understanding the pharmacokinetic profile of an opioid drug is vital to therapeutic success, and mutations in human PK genes can alter the therapeutic efficacy of opioids. Oxycodone (**OXY**) is a semisynthetic opioid metabolized into noroxycodone (inactive, **NOR**) and oxymorphone (active, **OMOR**) by CYP450 enzymes, however there is limited knowledge regarding the transport of OXY and its metabolites in the brain. Our lab has observed that 30 minutes post oxycodone administration (1.25 mg/kg, i.p.), BALB/cJ mice show higher whole brain concentrations of oxycodone ($t(14)=-2.55$, $p=0.023$), noroxycodone ($t(14)=-1.917$, $p=0.076$), and oxymorphone ($t(14)=-2.06$, $p=0.058$) compared to the closely related BALB/cByJ substain. This observation mirrors previous findings indicating BALB/cJ mice show increased state-dependent CPP compared to BALB/cByJ. We aimed to discover genetic factors underlying this difference by quantitative trait locus (QTL) mapping whole brain OXY, NOR, and OMOR concentrations in a reduced complexity cross (**RCC**). Because BALB/cJ and BALB/cByJ substrains differ by only ~11,000 SNPs, insertions, and deletions, large genetic loci mapped in F2 studies are offset by dramatically reduced density of potentially causal variants. QTL mapping in 119 BALB/cJ x BALB/cByJ F2 mice (59F, 60M) identified 3 loci on chromosomes 5, 10, and 16 significantly associated with OMOR concentration. Oxymorphone is a bioactive metabolite at the mu opioid receptor, with 8x the potency of oxycodone. Candidate PK-related genes within these regions include 18 SLC genes, but no CYP450, ABCs, or UGT genes. Future studies will overlay these findings with OXY behavioral QTLs and cis-eQTLs to identify candidate genes for validation.