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QTL mapping for initial sensitivity to cocaine using an F2 intercross of low and high responder inbred strains

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Our lab previously published phenotype data for locomotor sensitivity to cocaine in a panel of 45 inbred mouse strains. Initial locomotor sensitivity to cocaine is a commonly used rodent phenotype that is thought to share similarities with initial sensitivity to psychostimulants in humans. We discovered significant variation across strains and estimated a heritability of 53% in this population, indicating substantial genetic contribution to the phenotype. We have generated two F2 mapping populations using four strains that represented low (FVB/NJ, LG/J) and high (PL/J, C57BL/6J) responders to cocaine. FVB/NJ x PL/J (N=516) and LG/J x C57BL/6J (N=538) F2s were phenotyped for initial locomotor response to cocaine, genotyped using polymorphic SNP markers and QTL mapping was performed using R/qtl. Mapping in the PL/J x C57BL/6J population revealed significant QTL on Chr 1, 13 and 14 and a suggestive QTL on Chr 8. QTL mapping in the FVB/NJ x PL/J population yielded only a suggestive QTL on Chr 3. Strategies currently underway for narrowing QTL regions and prioritizing candidate genes include assessment of haplotype patterns in the 45 inbred strain panel, elimination of regions with common phylogenetic ancestry between the parental inbred strains and prioritization of genes with differential expression using gene expression data from these inbred strains in seven brain regions in the drug reward pathway. Identification of genes for initial sensitivity to cocaine using mouse models can provide insight into the molecular pathways involved in initial drug response in humans and may ultimately guide novel preventative and therapeutic approaches.