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Identification of a genetic locus and environmental factors influencing initial cocaine sensitivity in C3H substrains

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Quantitative trait locus (QTL) mapping in inbred mice has been used for decades to identify genetic loci contributing to complex traits. These studies have been extremely successful in identifying regions of the genome associated with drug response and reward. However, the transition from QTL to quantitative trait genes (QTGs) and causal polymorphisms has been less successful due to issues with low mapping resolution and the presence of numerous polymorphisms among the more commonly used and divergent inbred mouse strains. More recently, the identification of polymorphic single nucleotide polymorphisms in inbred mouse substrains and tools for efficiently assessing substrain genotypes has opened up a new avenue for rapid identification of QTGs. In order to take advantage of these new tools, one needs only to identify phenotypic differences in inbred substrains and conduct QTL mapping. Genetic complexity in substrain crosses is greatly reduced, limiting the number of causal loci (usually one) and the number of polymorphisms that must be interrogated at the identified QTL. We have identified a significant difference in initial cocaine-induced locomotor activation in C3H/HeJ and C3H/HeNTac substrains. We will present preliminary mapping data from an F2 cross between these substrains that identifies a locus on Chr 19. We will describe our use of whole-genome sequencing and phenotype data from two additional C3H substrains to identify the most likely causal polymorphism. We will also discuss potential environmental factors that could influence behavioral differences in these two substrains including maternal effects and striking differences in the gut microbiome.