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Identification of modifiers of MA intake in the presence of the high risk *Taar1*$^{m1J/m1J}$ genotype

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A single nucleotide, non-synonymous mutation in the trace amine-associated receptor 1 (*Taar1*) gene increases risk for methamphetamine (MA) intake in mice. The mutant allele (*Taar1*^{m1J}) codes for a non-functional receptor. To identify genetic modifiers that impact MA intake in mice that possess the high risk *Taar1*$^{m1J/m1J}$ genotype, we selectively bred high (MAH) and low (MAL) MA intake lines from a population of *Taar1*$^{m1J/m1J}$ individuals with a genetically heterogeneous background. Prefrontal cortex (PFC), nucleus accumbens (NAc) and ventral midbrain (VMB) were collected from the terminal S5 generation mice for RNA-seq analysis (n=12/line/sex/region). Data extracted included Differential Expression (DE), Differential Variability (DV; a surrogate for co-expression) and Differential Wiring (DW). Across all regions, there were ~300 DE genes (FDR<0.05); however, in no region did the DE genes show an enrichment in a GO category or pathway analysis (IPA). For the VMB DV genes ($p<10^{-4}$), there was a significant enrichment in a number of ontologies, including hormone activity (FDR<4 x 10^{-3}) and extracellular region (FDR<1 x 10^{-2}). Genes in the former category included *Pmch, Pomc, Gh, Prl & Inhba.* Genes in the latter category included hormone-related genes, such as *Scg5*, involved in hormone processing. An extracellular region signal for DV genes was found in the NAc and PFC, albeit weaker (FDR<0.1). *Pomc* was found in the extracellular ontology across all regions. These data are of particular interest, because the μ-opiate receptor partial agonist buprenorphine reduces MA intake. Support: NIH/NIDA-U01DA041579 (TP, RH), NIH/NIDA-R01DA046081 (TP, RH); Department of Veterans Affairs I01BX002106 (TJP).