Finding Candidate Genes for Addiction Within the Brain’s Reward System

Background
• The brain’s reward system is heavily dependent on the dopaminergic pathway.
• Major brain regions involved include the Ventral Tegmental Area (VTA), Amygdala, Nucleus Accumbens, Hippocampus and Frontal Lobe.
• The VTA is responsible for dopamine production, the Amygdala and Nucleus Accumbens deal with the emotional response to a stimulus after a rise in dopamine levels, the Hippocampus stores this response as a memory and the Frontal Lobe decides what further actions to take, debating whether or not the reward is worth any possible consequences.
• Addiction becomes dangerous when dopamine signals grow weaker and the subject becomes more reliant on the source of the reward for pleasure, at the same time, the subject’s ability to quit the addiction is further weakened as the Frontal Lobe becomes less active.

Methods
• The Allen Brain Atlas database (http://www.allenbrain.org) was used to obtain a large list of active genes for each of the five brain regions by contrasting them with gray matter in a differential search. This provided data for 6 different donors (H0351.2001, H0351.2002, H0351.1009, H0351.1012, H0351.1015, H0351.1016).
• Venn diagrams (http://bioinfogp.cnb.csic.es/tools/venny/) were then used to find the genes expressed in each brain region that were common to all donors, as well as to find genes only expressed in individual donors.
• These gene lists of similar and different genes were then analyzed in GOstat (http://cbl.cmbi.ru.nl/cgi-bin/gostat) and DAVID (https://david.ncifcrf.gov).
• Genes that formed functional groups with a direct connection to the dopaminergic pathway were then filtered to form a list of genes of interest, which were then further researched with STRING (http://string-db.org) and NCBI (http://www.ncbi.nlm.nih.gov) to identify interacting partners and potential pathways.
• Genes with a consistently high fold-change value for all the donors were then taken for each target region, and researched via STRING and NCBI as well.
• GeneNetwork (http://www.genenetwork.org/web/go.py) was used to identify co-occurring traits for the candidate genes.

Conclusions
• We identified genes directly related to the Dopaminergic pathway: OPRM1, DRD1, GNA1L1 and SLC6A3.
• Genes: TH and NTRK1 may have some relation to nicotine dependence but the mode of interaction is not established at this time.
• The enrichment results all had somewhat weak clustering, though the P-values are still significant, ranging from 10^-3 to 10^-5.
• The genes of interest with the highest fold-change values are SLC18A2, SLC6A3 and TH and while the genes with the lowest fold-change values are KCNS1, SBSN and GDA.
• Correlation analyses identified traits that have a greater range of expression in the dopamine receptor, DRD2 as compared to the dopamine transporter, SLC6A3.
• GNA1L1 and OPRM1 correlate with the protein expression of dopamine transporters and receptors.
• Taken together, these findings support the hypothesis that dopamine signals may be inhibited thereby leading to a greater dependence on drugs, especially related to activity via OPRM1.