Meta-analysis of comparisons to non-dependent misusers implicates *CD244* involvement in opioid dependence

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Opioid dependence, a severe addictive disorder and major societal problem, is moderately heritable. We conducted a meta-analysis of available genome-wide association study (GWAS) data in European ancestry individuals from three sources. Two sources included opioid dependent cases and non-dependent opioid misuser controls, a GWAS of Heroin Dependence (N=1951 cases; N=74 controls) and the Yale-Penn genetic studies of opioid, cocaine, and alcohol dependence (N=1043 cases; 135 controls). The third source included opioid dependent cases from the Urban Health Study (N=711 cases) and non-dependent misuser controls from the Study of Addiction: Genetics and Environment (N=393 controls). Meta-analyses of genotyped and 1000 Genomes imputed variants (MAF $\geq$.01) from these three sources identified a block of SNPs in high linkage disequilibrium (LD) that reached genome-wide significance. The most highly associated SNP, rs4656938 (p=5.10E-9; beta=0.43), is located in *CD244* which encodes the natural killer cell receptor 2B4. SNPs in this association signal have been established as expression QTLs and implicated as putative enhancers across a number of brain regions. A study that examined gene expression changes occurring in a murine model of chronic neuropathic pain found *CD244* expression to be acutely elevated in microglia. *CD244* has been implicated in gene network analyses focusing on data from genetic studies of alcohol, smoking, and opioid addiction phenotypes. Our findings provide further support for comparisons of opioid dependent cases with non-dependent opioid misusers to identify polymorphisms and genes implicated in opioid dependence. Our results specifically highlight the involvement of *CD244* and are consistent with data implicating the involvement of immunologic pathways in the pathophysiology of opioid dependence.