Copy Number Variants (CNVs) are large structural variants that can alter function by several mechanisms, including gene deletion and duplication, and thereby may alter susceptibility to Substance Use Disorders (SUDs). CNVs have been implicated in several neuropsychiatric diseases including autism, schizophrenia, and Alzheimer’s disease. The rarity or de novo nature of most CNVs impedes linkage to phenotypes; however even rare CNVs may be abundant in families and founder populations. Therefore, in this study, we identified recurrent CNVs (rCNVs) in American Indian tribes that are relatively low in genetic admixture but have high prevalence of SUD. CNVs were identified via Illumina SNP arrays in 400 Plains Indians and 320 Southwest Indians. All had been psychiatrically diagnosed via structured interviews (SADS-LA). Uniquely, we identified large (>200 kb) rCNVs that were abundant in both of two geographically separated American Indian tribes. A CNV at chromosome 6p21.33 was present in more than one in eight individuals in one of the populations and in more than one in four in the other, and multiple homozygotes were observed for that deletion. Haplotype and deletion breakpoint analyses showed that the recurrent CNVs derived from a common ancestor. Most individuals carried at least one rCNV, and CNV load ranged from 0 to 5. These rCNVs, including deletions and duplications encompassing various genes that may contribute to development of SUDs, are being evaluated for effect on transcriptome and linkage to behavior.