**Deletions in the SLC25A18 and ZNF490 Genes Associated with Alcohol Dependence—A Genome-wide Copy Number Variation Screen**

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**Background:** Genome-wide association studies of single nucleotide polymorphisms (SNPs) have yielded associations with addiction to various substances. However, all the published SNPs collectively account for a small proportion of estimated heritable risks for developing the disorders. Converging evidence show that copy number variations (CNVs) contribute to the development of various complex human diseases. We hypothesized that some of the “missing heritability” in alcohol dependence (AD) might be attributed to CNV.

**Methods:** We collected a total of 6,950 African-Americans (AAs) and European-Americans (EAs) of AD patients and screened controls, representing one of the largest known AD cohorts. We assayed all the samples using one million CNV probes on the Illumina HumanOmni1 arrays, and implemented multiple CNV calling algorithms, which have been demonstrated with increased CNV calling accuracies compared to any single algorithm alone. We carried out a genome-wide CNV screen to identify genes associated with AD using consensus CNV calls from the calling algorithms.

**Results:** Our findings showed that the AD patients contained more CNVs than controls \((P = 4 \times 10^{-23})\). The two most significant deletions associated with AD, \textit{SLC25A18} (corrected \(P = 4 \times 10^{-15}\)) and \textit{ZNF490} \((P = 9 \times 10^{-10})\), have been replicated in two American populations and validated through qPCR and Long PCR. The two novel AD associations show large risk effects \((\textit{SLC25A18 OR} = 7.41 \text{ and } \textit{ZNF490 OR} = 7.15 \text{ EAs})\). By comparison, the average OR of SNPs associated with mental illnesses was 1.45.

**Conclusion:** The \textit{SLC25A18} deletion is within the well-known “22q11.2 deletion” region, which has been associated with numerous AD-related behavioral problems and mental illnesses. This study, for the first time, identified an association of this region with AD, and fine-mapped the 8 million bp 22q11.2 region down to a 2,707 bp region in the \textit{SLC25A18} gene. The \textit{ZNF490} gene has been associated with AD-related psychiatric disorders. This study, for the first time, showed an association of a deletion in the \textit{ZNF490} gene with AD, and fine-mapped the signal to a 4,057 bp region of this gene.