Gene Expression Profiling in the Dorsolateral Prefrontal Cortex of Subjects with Completed Suicide and Substance Abuse

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Background

Although subjects with substance abuse are at increased risk for suicidal behavior, most genomic studies of suicide have excluded this group of patients, and little is known about the molecular basis of the association between substance abuse and suicidal behavior. The prefrontal cortex is the cerebral area responsible for decision making, and inhibition, functions that are altered in suicidal behavior. In addition, cognitive abilities associated with the prefrontal area, specifically the dorsolateral prefrontal cortex, are impaired in subjects with substance abuse.

Materials and methods

Total RNA was isolated (Qiagen RNAeasy) from the dorsolateral prefrontal cortex (BA9) of subjects who committed suicide and had substance abuse (N=22) and subjects who committed suicide but did not have substance abuse (N=21). Medical and forensic records were obtained from all subjects and structured interviews of family members were performed to obtain additional relevant information. After assessing RNA integrity, gene expression profiles were obtained using the HumanHT-12 v4 BeadChip Array (Illumina). Data was preprocessed by background adjustment and quartile normalization using GenomeStudio software v2011.1. Differentially expressed genes between groups were identified as those with an adjusted p-value lower than 0.01 and fold changes values >1.3 or <-01.3. We conducted molecular network enrichment analyses using Ingenuity Pathway Analysis (QIAGEN).

Results

We found 536 differentially expressed genes between groups (289 down-regulated, 247 up-regulated). These DEG's were enriched in the m-TOR signaling pathway, implicated in the regulation of synaptic proteins, the Cdc42 pathway, a key organizer of the actin skeleton that has been associated to alterations in the formation of dendritic spines in schizophrenia, and the calcium signaling pathway. Further studies are necessary to validate these results and assess the relevance of these pathways in the physiopathology of substance abuse and its implications for suicide.