Effects of smoking during pregnancy on the prenatal cortical transcriptome

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Cigarette smoking during pregnancy is a major public health concern. While there are well described consequences in early child development, there is very little known about the effects of maternal smoking on human cortical biology during prenatal life. We therefore performed a genome-wide differential gene expression analysis using RNA sequencing (RNA-seq) on prenatal (N=33; 16 nicotine-exposed) as well as adult (N=207; 57 active smokers) human post-mortem prefrontal cortices. Nicotine exposure during the prenatal period was directly associated with differential expression of 14 genes: in contrast, during adulthood, despite a much larger sample size, only 2 genes showed significant differential expression (FDR<10%). Moreover, 1,315 genes showed significantly different exposure effects in the pre- versus post-natal human cortex largely driven by prenatal differences that were enriched for pathways previously implicated in nicotine addiction and synaptic function. These genes were further enriched for genes implicated in syndromic autism spectrum disorder (ASD) and significantly differentially expressed as a set in brains of postmortem patients with ASD compared to controls. Lastly, to better untangle the effects of nicotine exposure and nicotine-predisposing genetic variants in the brain, we integrated expression quantitative trait loci to uncover novel *cis*-regulatory effects for nicotine dependence on local transcription in the adult human brain (N=237), including associations with *COMMD7* ($p=1.56\times10^{-9}$), *CYP2T2P* ($p=1.17\times10^{-7}$), and *AXL* ($p=4.76\times10^{-5}$). These results underscore the enhanced sensitivity to the biological effect of nicotine in the developing brain and offer novel insight into the effects of nicotine exposure's on the prenatal human brain and the independent functional consequences of genetic risk variants for nicotine dependence. They also begin to address the relationship between *in utero* exposure to nicotine and the heightened risk for the subsequent development of neuropsychiatric disorders.