Title: Placental gene expression, obstetrical history and polygenic risk for schizophrenia

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Abstract text:

Early life events associated with placental pathophysiology influence later susceptibility to many adult diseases and may contribute to define the environmental context in which genes enhance risk for complex disorders like schizophrenia. Here we analyze the role of intrauterine and perinatal complications (Early Life Complications, ELCs) and placental gene expression in modulating the association of schizophrenia with genomic risk, as measured with polygenic risk scores (PRS) based on GWAS significant variants. We found that PRS interacts with ELCs on case-control status, in three independent samples from USA, Italy and Germany (n= 1693, p= 6e-05); in each sample the variance of schizophrenia explained by PRS is multiplicatively higher in the presence of a history of ELCs compared with the absence of ELCs. The relationship between PRS and ELCs is replicated in two independent samples of only cases from Germany and Japan (n=2038, p=1e-04). The gene-set based on the schizophrenia loci interacting with ELCs is highly expressed in multiple placental tissues (p<0.001) and dynamically regulated in placental samples from complicated, in comparison with normal, pregnancies (p<0.05). These differences are significantly greater in placentae from male compared with female offspring (p<10^-8). GWAS SNPs marking the loci containing genes highly expressed and dynamically modulated in placenta (PlacPRS genes) drive the interaction between PRS and ELCs (p=0.002), while PRS constructed from the remaining loci do not interact with ELCs (NonPlacPRS, p=0.60). Pathways and biological functions associated with NonPlacPRS genes are reminiscent of previous analyses about schizophrenia risk-genes, while PlacPRS genes implicate an orthogonal biology, with roots in the fetal/placental response to hypoxic stress. Our data suggest that the most significant schizophrenia
GWAS variants contribute to risk by converging on a developmental trajectory sensitive to ELCs and altered placental gene expression, which may underlie the male preponderance of schizophrenia and offer new insights into primary prevention.