Results: PRS interacts with ELCs on case-control status, in the three independent samples from USA (p= p=0.004), Italy (p=0.018) and Germany (p=0.018); 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 such events. The relationship between genomic risk and ELCs is further replicated in the two independent samples of only cases from Germany (p=0.047) and Japan (p=0.044). The gene-set based on PRS 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). The interaction between PRS and ELCs is largely driven by PlacPRS genes (p=0.002); 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.
Discussion: Our data suggest that the most significant schizophrenia GWAS variants contribute to risk at least partly by converging on a developmental trajectory sensitive to ELCs and altered placental gene expression. The sex-associated effects on placental transcription suggest that the male preponderance of schizophrenia may arise from gene-environment interactions that influence placental biology. These results highlight placental health as a new public health frontier for primary prevention, particularly in high-risk males.

O4.8. VULNERABLE PERIODS FOR COGNITIVE DEVELOPMENT IN INDIVIDUALS AT HIGH GENOMIC RISK OF SCHIZOPHRENIA

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Background: 22q11.2 Deletion Syndrome (22q11.2DS) is caused by the deletion of approximately 60 genes on chromosome 22 and represents one of the strongest known genetic risk factors for schizophrenia. Approximately 1 in 4 adults with 22q11.2DS are diagnosed with schizophrenia spectrum disorders, presenting with psychotic symptomatology analogous to that exhibited in idiopathic schizophrenia.
Cognitive deficits are a core feature of schizophrenia. 22q11.2DS presents a valuable model for understanding vulnerable periods of cognitive development which may be associated with psychosis development. Most previous studies report greater deficits in older individuals with 22q11.2DS than younger individuals but these studies have often focused solely on IQ, neglecting other neurocognitive domains associated with schizophrenia. Additionally, many studies of 22q11.2DS have not included adults, missing a crucial group at increased risk for schizophrenia. The first aim was therefore to examine whether there are increasing deficits in cognitive functioning on a wide range of domains in 22q11.2DS across developmental stages (children, adolescents and adults) compared to typically developing (TD) controls. The second aim was to take into account the presence of a psychotic disorder, and whether this explained variance in functioning.
Methods: We conducted the largest study to date of neurocognitive functioning beyond IQ in 22q11.2DS. This work was the result of international collaboration across 3 sites. The same battery of tasks measuring processing speed, attention and spatial working memory were completed by 219 participants with 22q11.2DS and 107 TD controls. Wechsler IQ tests were completed, yielding Full Scale (FSIQ), Verbal (VIQ) and Performance IQ scores (PIQ). An age-standardised difference score was produced for each participant taking into account TD control performance. The average performance of children (6–10 years), adolescents (10–18 years) and adults (18–56 years) was compared using an ANOVA approach. No children or adolescents reached diagnostic criteria for a psychotic disorder, but 13% of adults with 22q11.2DS were either diagnosed with a DSM-IV psychotic disorder. The cognitive performance of adults with or without a psychotic disorder was compared with independent t-tests with correction for unequal variance.
Results: Children and adults with 22q11.2DS displayed a greater deficit in working memory than adolescents (p=0.017 and p<0.001 respectively). Adults displayed greater deficits in FSIQ and PIQ than adolescents (p=0.018 and p=0.001 respectively). Adults diagnosed with a psychotic disorder displayed a greater deficit in VIQ than those without a psychotic disorder (p=0.040).
Discussion: Magnitude of cognitive deficit in individuals with 22q11.2DS varied by cognitive domain and developmental stage. There were specific deficits in working memory, PIQ and FSIQ in adults with 22q11.2DS compared to children and adolescents. The lack of differences between children and adolescents contradicts previous research which proposes that older children exhibit greater cognitive deficits, and suggests that there may be a longer developmental window to intervene and maintain cognitive functioning in a group at high genomic risk of schizophrenia. Adults with 22q11.2DS and psychotic disorder had a greater deficit in VIQ, which supports previous research. This international sample provides unique insights into cognitive functioning in 22q11.2DS across developmental stages.

O5. Oral Session: Comorbidity

O5.1. CLOZAPINE AND LONG-TERM MORTALITY RISK IN PATIENTS WITH SCHIZOPHRENIA: PRELIMINARY RESULTS FROM A META-ANALYSIS

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Background: Patients with schizophrenia have a high mortality risk. The role of clozapine in the long-term mortality risk is insufficiently known. The objectives of the current study were to determine in i) all-cause long-term mortality rates and ii) specific-cause mortality rates and ratios in patients with schizophrenia with and without clozapine treatment.
Methods: We systematically searched EMBASE, MEDLINE and PsycINFO and included studies that used a long-term follow-up design (i.e., ≥52 weeks) and reported on mortality in adults diagnosed with schizophrenia-spectrum disorders receiving clozapine treatment.
Results: Altogether, 23 studies fulfilled our criteria, reporting on 1,166 deaths during 203,231 patient years for patients treated with clozapine. Pooling five cohort studies that included sufficient sample sizes and length of follow-up, we found an unadjusted mortality rate of 7.34 per 1,000 patient years (95%CI=4.39–10.28). Long-term, crude mortality rate ratios were significantly lower in patients treated with clozapine compared to patients without clozapine treatment (mortality rate ratio=0.59, 95%CI=0.43–0.81, p-value<0.001) as well as compared to other antipsychotic medications (mortality rate ratio=0.61, 95%CI=0.45–0.84, p-value=0.002). We found incomplete and inconsistent reporting of specific-cause mortality rates. Statistical heterogeneity was high in all analyses.
Discussion: Future studies with substantial length of follow-up and uniform reporting of confounders are needed to validate these findings of a significantly lower mortality risk in patients using clozapine, in particular for the risk of cardiovascular mortality.