profiles at the onset of psychosis can discern the likely trajectory symptoms over the subsequent 5 years of illness.

Methods: The study sample consists of 200 first-episode psychosis cases (ICD-10 codes: F20-F29 or F30-F33) aged 18–65 years who presented to SLAM (South London and Maudsley NHS Trust) mental health services between the 1st of January 2010 and the 1st of January 2015. Patients were subsequently recruited to the GAP study. Patients were followed-up electronically for 5 years post recruitment using the CRIS research platform. RNA samples were collected at the baseline timepoint via PAXgene blood tubes and interrogates, using the Illumina HumanHT-12.v4 beadchip array. Samples were run at the National Institute for Health Research’s (NIHR) Biomedical Research Centre for Mental Health (BRC-MH) at the Institute of Psychiatry, Psychology and Neuroscience. A total of 4756 probes passed a stringent quality control across the 200 samples.

Results: CRIS data pertaining to the GAP cohort was interrogated for information on clinical symptoms over a 5-year period using text-mining and natural language processing apps that represent over 70 different dictionary definitions of psychotic and affective symptoms. Confirmatory factor analysis was used to reduce this to a much smaller set of orthogonal symptom dimensions which were then the subject of a genetic interrogation using gene expression data. The analysis was conducted using a statistical learning framework which combines Elastic net penalised regression methodology with K-fold cross-validation (via the GLMnet package in R). This identified gene transcripts that were predictive of longer term symptom trajectories in half of the available sample. The veracity of the model was further validated using the second withheld portion of the sample.

Discussion: The results of this discovery phase may provide a rationale for subsequent multi-modal investigations whose aims will be to further enrich the biomarker signature and to also understand the molecular mechanisms that sustain them.

O4.6. GENOME-WIDE ASSOCIATION STUDY, HERITABILITY ESTIMATION AND POLYGENIC RISK ANALYSIS OF SUSCEPTIBILITY TO INFECTIONS IN 65,534 INDIVIDUALS WITH SEVERE MENTAL DISORDERS AND POPULATION CONTROLS

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Background: Infections are one of the major disease burdens internationally; however, the genetic architecture of infections is largely unknown. The human leukocyte antigen (HLA) loci have been implicated in susceptibility for infections; however, to date, largescale HLA type and genome-wide association studies (GWAS) of infections have been lacking. We aim to investigate the genetic architecture of infections with GWAS of single-nucleotide polymorphisms (SNPs) and HLA types, including associations with mental disorders.

Methods: We conducted case-cohort association analysis using both SNP’s and HLA types from a Danish population-based sample born after 1981 comprising of 65,534 unrelated Danish individuals. All individuals were linked utilizing nationwide population-based registers with virtually complete registration of all hospital contacts for infections from birth, where 28,472 (43%) individuals had ≥1 infection requiring hospitalization. Among the 45,889 cases with mental disorders, a total of 21,728 (47%) cases had hospitalizations for infections, whereas among the 19,645 individuals with no severe mental disorders, a total of 6,744 (34%) cases had hospitalization for infections. All analyses were adjusted for age, sex, and principal components.

Results: We will present GWAS findings of the overall susceptibility for acquiring infections among individuals with severe mental disorders exploring differences to population controls. Furthermore, we will present SNP heritability of acquiring infections among individuals with severe mental disorders exploring differences to population controls. Moreover, we will present findings from association analysis of HLA types investigating the role of HLA alleles in susceptibility to infections and mental disorders. Lastly, we will present results on possible gene-infection interaction regarding the risk of mental illness.

Discussion: Our findings will illuminate the genetic architecture of acquiring infections, and the genetic associations with mental disorders exploring the possible genetic component of the known association between infections and severe mental disorders, such as schizophrenia. Furthermore, we will for the first time in a large population based study explore the associations with HLA alleles to infections and severe mental disorders.

O4.7. PLACENTAL GENE EXPRESSION, OBSTETRICAL HISTORY AND POLYGENIC RISK FOR SCHIZOPHRENIA

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Background: Early life events influence later susceptibility to many adult diseases and may contribute to define the environmental context in which genes enhance risk for complex disorder like schizophrenia. Here we analyze the role of intrauterine and perinatal environment in modulating the association of schizophrenia with genomic risk.

Methods: We evaluated whether genomic risk for schizophrenia interacts with intrauterine and perinatal complications (Early Life Complications, ELCs) on case-control status, in three independent samples of healthy subjects and patients with schizophrenia from USA (n=501), Italy (n=273) and Germany (n=919). We further analyzed the relationship between genomic risk and ELCs in two samples of only patients with schizophrenia from Germany (n=1019) and Japan (n=172). Genomic risk was measured with polygenic risk profile scores based on GWAS-significant alleles (PRS), while ELCs history was assessed with the McNeil-Sjostrom Scale. We tested whether genes overlapping the schizophrenia loci interacting with ELCs are enriched in placenta and differentially expressed in placental samples from complicated pregnancies, in 8 independent placental datasets. Finally, we evaluated whether GWAS SNPs marking loci containing genes highly expressed and dynamically modulated in placenta (PlacPRS genes) drive the interaction between PRS and ELCs, and performed pathway analyses on PlacPRS genes.

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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 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 IQ 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.