imaging genetics approaches currently used in the pursuit of the pathophysiology of schizophrenia.

T185. DIFFERENTIAL ACTIVITY OF TRANSCRIBED ENHANCERS IN THE PREFRONTAL CORTEX OF 592 CASES WITH SCHIZOPHRENIA AND CONTROLS

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Background: Transcription at enhancers is a widespread phenomenon, which produces so-called enhancer RNA (eRNA) and occurs in an activity dependent manner. The role of eRNA and its utility in exploring disease-associated changes in enhancer function and the downstream coding transcripts that they regulate is however not well established. We here used transcriptomic and epigenomic data to interrogate the relationship of eRNA transcription to disease status and how genetic variants alter enhancer transcriptional activity in the human brain.
Methods: We combined RNA-seq data from 537 post mortem brain samples from the CommonMind Consortium with cap analysis of gene expression and enhancer identification, using the assay for transposase-accessible chromatin followed by sequencing.
Results: We find 118 differentially transcribed eRNAs in schizophrenia and identify schizophrenia-associated gene/eRNA co-expression modules. Perturbations of a key module are associated with the polygenic risk scores. Further, genetic variants affecting expression of 927 enhancers, which we refer to as enhancer expression quantitative loci or eeQTLs, are identified. Enhancer expression patterns are consistent across studies, including differentially expressed eRNAs and eeQTLs. Combining eeQTLs with a genome-wide association study of schizophrenia identifies a genetic variant that alters enhancer function and expression of its target gene, GOLPH3L.
Discussion: Here, we expanded the scope of the CommonMind Consortium to interrogate enhancer function in schizophrenia, to examine how genetic variation affects enhancers, and to evaluate specific effects on enhancer and gene expression for previously identified schizophrenia risk variants. Our novel approach to analyzing enhancer transcription is adaptable to other large-scale, non-poly-A depleted, RNA-seq studies.

T186. ASSOCIATION BETWEEN POLYMORPHISMS OF THE NEUREGULIN 1 (NRG1) GENE AND SCHIZOPHRENIA

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Background: The dysfunction of neuregulin 1 (NRG1) is one of the plausible hypotheses for the pathogenesis of schizophrenia. The neuregulin 1 (NRG1) is located on chromosome 8p, as suggested by multiple linkage studies. The aim of this study is to clarify the contribution of polymorphisms of the neuregulin 1 (NRG1) with schizophrenia
Methods: After informed consent was obtained, 100 schizophrenia patients and 100 control subjects were enrolled in this study. All subjects were administered the Diagnostic Interview for Genetic Studies (DIGS) (National Institute of Mental Health-Molecular Genetics Initiative, 1992; Nurnberger et al., 1994) by a research assistant with extensive training in this interview. Blood samples were collected in anonymously identified 10-ml Vacutainer tubes (Becton Dickinson). DNA was prepared by a modified SDS/Proteinase K procedure (Gusells et al., 1979). We genotyped polymorphism neuregulin 1 (NRG1) with the PCR-RFLP methods. The PCR products were digested by restricted enzyme.
Results: We observed a significant association between the polymorphism neuregulin 1 (NRG1) and the schizophrenia (Chi-Square Test P= 0.0449).
Discussion: The NRG1gene was originally identified as a susceptibility gene for schizophrenia by using a combination of a linkage and association approaches based on microsatellite markers and then using SNPs after microsatellite at risk haplotypes were identified. We found there is the frequency of the polymorphism of neuregulin 1 (NRG1) was significantly increased in schizophrenia patients. This allelic association suggests that the functional polymorphism neuregulin 1 (NRG1) may play a role in susceptibility to schizophrenia. Further study with larger sample sizes is required.

T187. ALTERED DNA METHYLATION OF THE OXYTOCIN RECEPTOR GENE IS ASSOCIATED WITH SUSCEPTIBILITY TO PSYCHOSIS AND ANHEDONIA-ASOCIALITY IN FEMALES: EPIGENETIC EVIDENCE IN RECENT-ONSET SCHIZOPHRENIA AND ULTRA-HIGH RISK FOR PSYCHOSIS

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Background: Oxytocin is one of the key hormones involved in human social and emotional processing. In this regard, abnormal functioning of the oxytocin system has been suggested to influence on the clinical manifestation of schizophrenia, especially negative symptoms. The aim of the present study was to investigate epigenetic modification of the oxytocin receptor gene (OXTR) and its association with negative symptoms in individuals with recent-onset schizophrenia (SCZ) and at ultra-high risk (UHR) for psychosis.
Methods: Sixty-four SCZ patients (< 5 years of duration of illness; 25 men, 39 women), 46 UHR individuals (27 men, 19 women), and 98 healthy controls (HCs; 46 men, 52 women) participated in the present study. DNA methylation was quantified from peripheral blood using pyrosequencing at CpG sites in OXTR intron 1 (hg19, chr3: 8,810,729–8,810,845) and exon 3 (hg19, chr3: 8,809,281–8,809,534). The severity of negative symptoms in clinical groups was measured using the Scale for the Assessment of Negative Symptoms (SANS) and Scale for the Assessment of Positive Symptoms (SAPS).
Results: A multivariate analysis of covariance revealed significant differences in OXTR methylation between groups ($F = 16.00$, $p < 0.001$) and gender ($F = 2.84$, $p = 0.025$). Compared to HCs, both UHR and SCZ participants showed lower levels of OXTR intron 1 methylation, particularly at CpG site -934 upstream of the OXTR start codon (HCs = 47.3 ± 4.1 [mean ± SD], UHR = 38.8 ± 4.8, SCZ = 40.2 ± 5.3; $F = 73.74$, $p < 0.001$). Besides, female participants showed higher OXTR intron 1 methylation at CpG site -934 than male participants (male = 42.3 ± 6.1, female = 44.1 ± 5.8, $F = 9.08$, $p = 0.003$). Multiple linear regression analysis with clinical symptoms demonstrated that the degree of DNA methylation at CpG site -934 was significantly associated with the SANS anhedonia-asociality subscale scores in the entire group of female UHR and SCZ participants (beta = -0.44, $p = 0.001$).
Discussion: The present study demonstrated decreased OXTR methylation in both UHR and SCZ individuals compared to HCs. Furthermore, the severity of anhedonia-asociality was significantly associated with the degree of OXTR methylation in female UHR and SCZ individuals. These findings suggest that epigenetic aberration of OXTR may confer susceptibility to schizophrenia spectrum psychosis and influence the early pathogenesis of schizophrenia prior to the onset of overt psychosis, particularly in females.