Methods: Studies published between January 2010 and March 2017 were identified using a customized querying strategy. Identified gene-association studies were included in the review and meta-analysis if they: 1) were case-control or family-designed studies with polymorphisms detected in schizophrenia or schizoaffective patients, 2) provide sufficient data to perform meta-analysis, and 3) were not genome-wide association studies (GWAS). Random-effects meta-analysis was performed on polymorphisms with four or more independent studies.

Results: Raw data of 1711 studies included in the SzGene database were integrated with 1368 studies identified from our systematic literature search. Random-effects meta-analysis were applied to 540 polymorphisms with at least four studies and 89 of these polymorphisms were nominally associated with SZ (unadjusted p < 0.05). After bonferroni correction, 12 polymorphisms remained statistically significant, including five associations not reported in the most recent Psychiatric Genomics Consortium schizophrenia GWAS: 1) rs11098403, p = 1.45e-10, odds ratio = 0.65; 2) rs12807809, p = 7.04e-06, odds ratio = 0.91; 3) rs910694 in PDE4B: p = 1.05e-05, odds ratio = 0.77; 4) rs1801133 in MTHFR: p = 2.99e-05, odds ratio = 1.13 and 5) rs1602565: p = 7.73e-05, odds ratio = 1.11.

Discussion: Our results provide a comprehensive and up-to-date review of candidate gene association studies in schizophrenia. Findings complement results from GWASs in schizophrenia but also expand the current list of candidate loci for schizophrenia.

F193. DYSREGULATION OF RETINOID SIGNALLING IN SCHIZOPHRENIA OBSERVED IN WHOLE GENOME SEQUENCE ANALYSIS

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Background: Retinoic acid (RA) is intrinsically linked to neurodevelopment and has been implicated in schizophrenia (SZ). This is supported by preliminary trials of a retinoid receptor agonist, Bexarotene, as an adjuvant and the association of five common variants in proximities to members of this pathway at genome wide significance. In addition to these high frequency variants with small effect size, we suspect that this pathway is also affected by rare variants with much higher impact. We aimed to examine the burden of variants in retinoid loci in schizophrenia along with its potential consequences for clinical practice.

Methods: Whole genome sequencing was performed on SZ cases (N=331) and non-psychiatric controls (N=167). Cases were further clustered by cognitive measures to derive the cognitive deficit (CD; N=166) and cognitively spared (CS; N=165) subtypes. Disease and subtype associated genomic variation was then analysed in a panel of 129 genes selected for involvement in RA biology (Molecular Signatures Database). Rare variation was aggregated at the gene level using the optimal unified sequence kernel association test (SKAT-O). Clinical metadata was further examined for each case with a rare putative high impact loss of function variant in a RA panel gene predicted using SnpEff. The rare variant burden on target genes of RA receptor binding in SZ was investigated by logistic regression of variants mapped to consensus 5 base pair spaced direct repeat (DR5) retinoic acid response element (RARE) motifs.

Results: Gene level rare variant association uncovered suggestive associations with SZ (P < 0.01) for three retinoid genes – RBP3, ADH1C and RPE65. In addition, a stronger signal was detected overall for CD cases implicating four additional genes including the RA receptors RARB (P = 1.1 x 10-3) and RARG (P = 9.2 x 10-3). SZ patients with a rare high impact genotype predicted in a RA panel gene were more likely to have serious symptomology as defined by a global assessment of functioning (GAF) score below 50, P = 7.1 x 10-3 (Two-Tailed Fisher’s Exact Test). We also found evidence of an increased burden of rare variants within predicted DR5-RARE in SZ (P = 0.017, odds ratio [OR] = 1.094, 95% confidence interval [CI] = 1.023-1.186), however, there was no significant difference between the cognitive subtypes (CD/CS, P = 0.8, OR = 1.002, 95% CI = 0.961-1.045).

Discussion: Our findings suggest that RA mediated control of gene expression is heterogeneously disrupted in SZ by rare variants in DR5-RARE motifs. Strong signals in the context of our sample size further support the possibility of enrichment of rare loci in genes involved with RA biology, particularly in CD cases with impaired cognition. Moreover, we identified a subset of patients with likely high effect size genotypes in the RA pathway. Future work will examine whether these high-risk patients would benefit from retinoid based pharmacological intervention.

F194. ASSOCIATION STUDY BETWEEN TREATMENT RESPONSE OF AMISULPRIDE AND DOPAMINE D3 RECEPTOR GENE POLYMORPHISMS

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Background: The aim of this study is to evaluate the association between rs6280 and rs905568 genetic polymorphism of DRD3 gene and the treatment response of amisulpride.

Methods: After six weeks treatment of amisulpride, 125 schizophrenia patients were interviewed based on the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression-Severity (CGI-S). The genotyping for rs6280 and rs905568 was performed using TaqMan single nucleotide polymorphism (SNP) genotyping assay.

Results: There was no significant difference in the frequency of genotype and allele of rs6280 between the responders and non-responders based on the total, positive, and general score of PANSS and CGI-S score. However, there was a significant association between this SNP and treatment response in the negative score of PANSS (p2 = 5.23, p = 0.022). There was no significant association between rs905568 and the response in positive, negative, general, and total PANSS score and CGI-S score.

Discussion: This is the first positive association study between DRD3 gene and the treatment response of negative symptoms to amisulpride in Korean schizophrenia patients. A larger scale research on more SNP of the DRD3 gene will make a progress in the study of pharmacogenetics on the treatment response of the amisulpride.

F195. ENRICHMENT OF PATHOGENIC VARIANTS ASSOCIATED WITH TREATABLE GENETIC DISEASES IN LARGE SCHIZOPHRENIA, BIPOLAR AND DEPRESSION COHORTS

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Background: Genetic diseases are individually rare but collectively common. Many genetic conditions can mimic mental health disorders, with
triggered by the mGluR5 antagonist 2-Methyl-6-(phenylethynyl)pyridine.

**Methods:** Using targeted next-generation sequencing, we screened schizophrenia (n=1132), bipolar (n=719) and major depressive disorder (n=195) patients for variants in genes associated with Niemann-Pick disease type C (NPC), Wilson disease (WD), homocystinuria (HOM) and acute intermittent porphyria (AIP), and compared the frequency of known and predicted pathogenic variants found to 123 136 samples from the gnomAD consortium.

**Results:** Our study is the first to explore the prevalence of NPC, WD, HOM and AIP gene variants in well-defined psychiatric cohorts. Among 2046 cases (male, n=1106; female, n=940), carrier rates of 0.93%, 0.98% and 0.20% for NPC, WD and HOM were seen, respectively. The carrier rate for NPC was marginally enriched in the SCZ cohort (1.1%) compared to general (95% CI, 0.007 - 0.021; p=0.084) and comparison (95% CI, 1.967 - 5.272; p=5.16e-05) populations. AIP affected rate of 0.29% was observed across the entire psychiatric cohort relative to the general (95% CI, 0.001 - 0.006; p=3.47e-13) and comparison (95% CI, 1.572 - 10.044; p=0.012) populations, an almost 300x enrichment in comparison to what is expected in the general population.

**Discussion:** An enrichment of known and predicted pathogenic variants associated with NPC and AIP was found in the psychiatric cohort, especially in SCZ patients. The results of this proof-of-principle study support that rare genetic disease variants, such as those associated with treatable IEMs, may contribute to the pathogenesis and treatment responsiveness of psychiatric disorders. Discovering genetic diseases in psychiatric patients will shift how health care is delivered to these vulnerable patients by addressing underlying conditions rather than masking symptoms with medications, and has the potential to especially help patients who don't respond to regular psychotropic medications. Further studies screening large psychiatric cohorts for pathogenic variants in a large panel of treatable IEM genes will reveal the full impact of such disorders for psychiatric patients.

**F196. DIFFERENTIAL EFFECTS OF MGLU5 RECEPTOR BLOCKADE ON BEHAVIOR, SCHIZOPHRENIA-RELEVANT GENE EXPRESSION AND NEURONAL ACTIVATION PATTERNS FROM DEVELOPMENT TO AGING MICE**

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**Background:** The glutamate system is implicated both in schizophrenic and mood disorders. Mice lacking metabotropic mGlu5 receptors (mGlu5 KO) display schizophrenia-like abnormalities. Additionally, mGlu5 antagonists represent promising alternative anxiolytics/antidepressants. However, the underlying age-specific molecular/cellular mechanisms are only partially understood. We aimed at identifying molecular alterations associated with a genetically induced mGlu5 deletion, which results in a schizophrenia-like phenotype. Additionally, we investigated age-specific effects of mGlu5 antagonists on emotional behaviour and c-Fos activation.

**Methods:** For analysis of mRNA and protein levels we performed Real-time RT-PCR and Western blot investigations in the hippocampus and prefrontal/frontal cortex (PFC/FC) of mice with a genetic deletion of the metabotropic glutamate receptor 5 (mGlu5), addressing key components of the GABAergic and glutamatergic systems. Additionally, we used classical behavioral tests for determining anxiety- and depression-like changes triggered by the mGlu5 antagonist 2-Methyl-6-(phenylethynyl)pyridine (MPEP). Finally, we used profiling of c-Fos expression, as marker of neuronal activity, induced by MPEP from postnatal day 16 (P16) to adulthood (P90).

**Results:** mGlu5 knockout (KO) mice showed a significant reduction of reelin, GAD65, GAD67 and parvalbumin mRNA levels, which is specific for the PFC/FC, and that is paralleled by a significant reduction of protein levels in male KO mice. We also analysed the main NMDA and AMPA receptor subunits, namely GluN1, GluN2A, GluN2B and GluA1, and observed that mGlu5 deletion determined a significant reduction of their mRNA levels, also within the hippocampus, with differences between the two genders. We measured age-specific alterations in emotional behaviour of mGlu5 KO mice, with marked increase of anxiety during aging. There was a remarkably conserved activation of the paraventricular nucleus of the hypothalamus, implicated in stress regulation, by MPEP at all investigated ages, whereas the extended amygdala was specifically activated in adulthood only.

**Discussion:** Our data suggest that neurochemical abnormalities impinging the glutamatergic and GABAergic systems may be responsible for the behavioral phenotype associated with mGlu5 KO animals and point to the close interaction of these molecular players for the development of neuropsychiatric disorders such as schizophrenia. These data could contribute to a better understanding of the involvement of mGlu5 alterations in the molecular imbalance between excitation and inhibition underlying the emergence of a schizophrenic-like phenotype and to understand the potential of mGlu5 modulators in reversing the deficits characterizing the schizophrenic pathology.

**F197. PROMOTING MYELIN REPAIR RESCUES MICE FROM SCHIZOPHRENIA-LIKE BEHAVIOR INDUCED BY SOCIAL ISOLATION**

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**Background:** Although pathological and genetic evidence suggest that oligodendrocyte (OL) or myelin deficits are associated with schizophrenia, the contribution of OL/myelin deficits to its etiology has not been clearly dissected, because OL/myelin abnormalities may be a concomitant phenomenon during the pathogenesis of schizophrenia.

**Methods:** Using olig2 ablation specifically in OLs (olig2 CKO) mice, we detected myelin development status and animal behaviors under normal condition or subjected to social isolation. We also examined the therapeutic effect of FDA-approved compounds, like quetiapine (an APD) or clemastine (a histamine antagonist) on animal behaviors.

**Results:** Our results demonstrated that deleting of olig2 led to impaired development of OLs and myelin deficit from postnatal day14 (P14) to P56, preferentially in cerebral cortex, and these young adult Olig2 KO mice showed anxiety-like behavior, motor skill learning deficit and cognitive deficit. Moreover, Olig2 CKO mice exhibited earlier social avoidance behavior than the WT littermates under prolonged social isolation, indicating that myelin deficit may enhance risk of schizophrenia upon environmental stress attacking. Interestingly, enhancing oligodendrocyte generation and myelin repair by quetiapine or clemastine successfully reversed the above phenotype.

**Discussion:** Taking together, promoting myelin repair may present a new therapeutic strategy against schizophrenia.

**F198. EFFECTS OF CANNABINOIDS ON A HUMAN OLIGODENDROCYTE CULTURE: IMPLICATIONS FOR SCHIZOPHRENIA**

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**Background:** Although pathological and genetic evidence suggest that oligodendrocyte (OL) or myelin deficits are associated with schizophrenia, the contribution of OL/myelin deficits to its etiology has not been clearly dissected, because OL/myelin abnormalities may be a concomitant phenomenon during the pathogenesis of schizophrenia.

**Methods:** Using olig2 ablation specifically in OLs (olig2 CKO) mice, we detected myelin development status and animal behaviors under normal condition or subjected to social isolation. We also examined the therapeutic effect of FDA-approved compounds, like quetiapine (an APD) or clemastine (a histamine antagonist) on animal behaviors.

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**Discussion:** Taking together, promoting myelin repair may present a new therapeutic strategy against schizophrenia.