depressive disorder, bipolar disorder, autism spectrum disorder, Alzheimer’s disease and Parkinson’s disease. The interactome is constructed with experimentally determined PPIs from BioGRID and HPRD databases and novel PPIs predicted using our High-confidence PPI Prediction (HiPPIP) model. We previously presented Schizophrenia Interactome constructed using HiPPIP and also showed that novel PPIs are highly accurate based on computational and experimental validations. We validated additional PPIs of cilia interactome here. We computed how closely connected cilia is to genes associated with neuropsychiatric diseases, through interactome and pathway analysis. Additionally, we analyzed drugs that proteins in the cilia interactome, and found that majority of these drugs are nervous system associated drugs.

Results: The ciliary protein interactome consists of 165 ciliary proteins with 1,011 known PPIs and 765 novel PPIs. We found the overlap between cilia and neurotrophic interactomes to be statistically highly significant. For e.g., cilium interactome has an overlap of 125 genes with schizophrenia interactome of which 26 are novel interactors of cilia, and has significant overlap with pathways relevant to schizophrenia. About 184 genes in the cilia interactome are targeted by 548 FDA approved drugs, of which 103 are used to treat nervous system diseases.

Discussion: Ciliary genes like DRD1 and DRD2 are implicated in neurotransmission and associated with schizophrenia. DRD1 has 4 novel interactors and DRD2 has 12 novel interactors that may have significant role in the pathology of mental disorders. Neuronal pathways associated with cilia interactome with high statistical significance such as dopamine signaling, eNOS signaling, synaptic long-term potentiation pathways are known to be associated schizophrenia. Wnt signaling and PCP signaling are also known to be associated with cilia mediated neurodevelopmental signaling, defects in these pathways contributing to schizophrenia. Novel interactions for cilia proteins validated by experiments have functional significance in association with cilia and neuronal disorders. For e.g., IFT88, a cilia protein required for cilia assembly, is critical for SHH signaling, cell cycle regulation and cerebellar development and is also associated with schizophrenia and bipolar disorder. CACNA11 is predicted to interact with DNAJ4 and MK51, both involved in transport of proteins required for ciliogenesis. GWAS studies show that CACNA11 is associated with schizophrenia. Taken together, the cilia interactome presented here provides novel insights into the relationship between ciliary protein function and neuropsychiatric diseases.

F201. KINASE NETWORK DYSREGULATION IN SCHIZOPHRENIA: IMPLICATIONS FOR NEW TREATMENT STRATEGIES

Eduard Bentea*, 1, Erica Depasquale1, Jarek Meller2, Zhexing Wen1, Robert E. McCullumsmith1

1University of Cincinnati; 2Cincinnati Children’s Hospital Medical Center; 1Emory University School of Medicine

Background: Disrupted-in-schizophrenia 1 (DISC1) is one of the most substantiated genetic risk factors for schizophrenia (SZ). A large array of animal studies supports an etiopathogenic role of DISC1, by linking it with regulation of processes such as synapse formation and neuronal development. However, much less is known regarding the involvement of DISC1 in human neurons. Induced pluripotent stem cells (iPSCs) generated from patients carrying the disease have emerged as powerful tools to study cellular dysfunction in a disease-relevant context. In this study, we investigated serine/threonine kinase network in a human iPSC model of DISC1-related SZ.

Methods: PamChip arrays evaluate kinase activity by measuring phosphorylation levels of a series of immobilized peptide sequences during exposure to kinases in the sample. We employed PamChip arrays to map the serine/threonine sub-kinome of neurally differentiated iPSCs generated from a patient with SZ presenting the frame-shift DISC1 mutation (D2-1), an unaffected family member without the mutation (C3-1), as well as of isogenic iPSC lines in which the mutation was either corrected in D2-1 (resulting in the cell line D2-R), or introduced in C3-1 (resulting in the cell line C3-M). Using a bioinformatics workflow that identifies kinase hits using a random sampling model, we identified kinases that emerged as common hits after comparing D2-1 with D2-R (changed after rescuing the mutation in the patient cell line) and C3-M with C3-1 (changed after introducing the mutation in the control cell line). We used the resulting kinase network to identify pathways, perturbagens, and drugs related to the disease phenotype.

Results: By comparing D2-1 to D2-R, 9 peptide sequences were identified to be differentially phosphorylated at a +/- 1.15 fold-change level. After assigning upstream kinases to these peptides and generating the random sampling model, we identified 3 kinase subfamilies which were over-represented in D2-1 vs. D2-R: TAO, KHS and 5’ adenosine monophosphate-activated protein kinase (AMPK). By comparing C3-M to C3-1, we could identify 13 peptide sequences differentially phosphorylated at a +/- 1.15 fold-change level. Mapping these sequences to upstream kinases and running the random sampling model, led to the identification of 9 kinase subfamilies over-represented in C3-M vs. C3-1: AMPK, TAO, BUD32, WNK, KHS, RAD53, CK1, NEK and MLK. By overlapping the results, we could identify a set of 3 kinase subfamilies (TAO, KHS, and AMPK) commonly changed between the two methods of comparison. Ingenuity pathway analysis identified post-translational modification, cell signaling, cell morphology, cell cycle, and cellular assembly and organization, as the top functions of the DISC1 kinase network.

Discussion: Kinases are potent modulators of intracellular signaling that control patterns of gene expression, cytoskeletal dynamics, function of neurotransmitter systems and cellular metabolism, which may be of relevance to the etiopathogenesis of mental disorders, such as SZ. Herein, we characterized the serine/threonine sub-kinome of neurally differentiated iPSCs from a patient with SZ presenting with a 4-bp deletion in DISC1. Using gene editing we created isogenic cell lines to either rescue the mutation in the patient cell line, or introduce the mutation in iPSCs obtained from an unaffected family member, to strengthen causality for the DISC1 mutation. This approach led to the identification of 3 kinase subfamilies as common hits of the DISC1 phenotype: TAO, KHS, and AMPK. Our unbiased approach led to the novel identification of kinases implicated in DISC1-related SZ. Further validation of these findings may open new avenues for treating this highly disabling neuropsychiatric disorder.

F202. ABNORMAL REMODELING PROCESSING IN NEURAL GPI-APS SECRETORY PATHWAY IN SCHIZOPHRENIA

Pitna Kim*, 1 James Meador-Woodruff2

1University of Alabama at Birmingham

Background: Abnormalities in post translational modifications (PTMs) such as glycosylation have become targets of schizophrenia (SCZ) research and are implicated in the neuropathophysiology of this illness. Glycosylphosphatidylinositol (GPI) attachment to proteins and glycoproteins events; proteins essential to cellular function, including neurotransmitter receptors, adhesion molecules, and enzymes, are all modified by GPI. Biosynthesis of GPI-APS occurs in the endoplasmic reticulum (ER). Once GPI-APS are synthesized, they are transported from the ER to the cell surface through the Golgi apparatus. Inositol deacylation of the GPI-APS by common PTMs. The GPI-anchored proteins (GPI-APS) play an essential role in many biological functions. GPI-APS is required for efficient export from the ER and acts a molecular mechanism for quality control of GPI-APS. The p24 complex binds specifically to GPI-APS and plays a role in their selective trafficking by sensing the status of the GPI anchor and to promote efficient ER exit of remodelled GPI-APS. In this study, we identified abnormalities of proteins associated with the ER exit of GPI-APS in SCZ. To address mechanisms of GPI-APS ER exit, we measured expression of proteins of the GPI-APS ER exit and targeting pathway. We also measured expression of GPI-APS which have been previously implicated in SCZ, including GPC1, NCAM, MDGA2 and EPHA1.
Methods: We assessed the total expression and subcellular localization of proteins involved in ER export processing of GPI-APs from the DLPFC of 15 matched pairs of SCZ and comparison subjects. Specifically, we measured levels of PGAP1 and Tm2p21 (p24). Additionally, we performed a Triton X-114 phase separation to distinguish between membrane-associated and cytosolic forms of protein substrates. We confirmed the sensitivity of each target GPI-AP to phosphatidylinositol-specific phospholipase C (PI-PLC), an enzyme that specifically cleaves GPI from GPI-APs.

Results: We found a significant decrease in p24 in total tissue homogenates and PGAP1 in an ER enriched fraction from subjects with SCZ. We also identified diminished sensitivity of the GPI-APs, GCPC1 and NCAM, to PI-PLC treatment in SCZ.

Discussion: Decreased PGAP1 in an ER enriched fraction in consistent with reduced inositol deacylation and potential dysfunction as the gatekeeper of GPI-AP ER exit in SCZ. This also suggests that the GPI-anchor is not correctly modified. Decreased p24 levels suggest downregulation of transport between the Golgi and the ER in SCZ. Additionally, we observed unchanged total level of GPI-APs in Triton X-114 phase separation, but a significant decrease in the amount of NCAM and GCPC1 that was sensitive to PI-PLC in SCZ. This finding may be consistent with abnormal GPI modification of these two candidate proteins. Together, these findings suggest dysregulation of the GPI-APs remodeling system in SCZ, which may impact the structure of the GPI-anchor for SCZ-relevant proteins like NCAM and GCPC1.

F203. A META-ANALYSIS OF MINOR PHYSICAL ANOMALIES IN FIRST-DEGREE UNAFFECTED RELATIVES OF PATIENTS WITH SCHIZOPHRENIA

Ozge Akgul1, Emre Bora2, Berna Binur Akkede2, Koksal Alptekin1
1Dokuz Eylul University; 2Dokuz Eylul University School of Medicine

Background: Neurodevelopmental abnormalities are common in schizophrenia. Minor physical anomalies (MPAs) are associated with abnormalities in neural development. Previous studies clearly demonstrated that MPAs are significantly increased in schizophrenia. However, the available evidence in unaffected relatives of patients with schizophrenia is contradictory.

Methods: A literature search was conducted between 1 JAN 1980 and SEP 2017 in PUBMED and SCOPUS. Random-effects model was used. Heterogeneity was tested with Q test and I2. The meta-analysis was conducted using OpenMetaAnalyst software.

Results: 16 studies were included in the meta-analysis. MPAs were significantly more common unaffected first-degree relatives of patients with schizophrenia (d=0.56, CI=0.40-0.73, p<0.001). There was a significant heterogeneity in distribution of effect sizes (Q=42.2, p<0.001). The level of this heterogeneity was medium in range (I2=64%). In meta-regression analyses, demographic variables were not significantly related with magnitude of the effect size.

Discussion: MPAs are associated with risk of schizophrenia. However, the level of heterogeneity suggests that risk of psychosis is associated with neurodevelopmental abnormalities in some but not all individuals. Findings also emphasize that resilience factors might be protecting many neurodevelopmentally impaired relatives of schizophrenia against having a full-blown psychotic disorder.

F204. THE DANISH HIGH-RISK AND RESILIENCE STUDY - VIA 7 - A PROSPECTIVE COHORTE STUDY OF 522 7 YEARS OLD CHILDREN BORN TO PARENTS DIAGNOSED WITH SCHIZOPHRENIA OR BIPOLAR DISORDER - RESULTS ON PSYCHOPATHOLOGY, COGNITION AND LIVING CONDITIONS

Anne Amalie Thorup1,2, Nicoline Hemager2, Ditte V. Ellersgaard2, Camilla Jerlang Christiani1
1University of Copenhagen; 2Mental Health Services – Capital Region of Denmark, Child and Adolescent Mental Health Centre, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research; 3Mental Health Centre Copenhagen

Background: Olfactory dysfunction has repeatedly been observed in individuals diagnosed with schizophrenia. The most stable and consistent finding on the behavioral level is that of smell identification deficits. However, the nature of olfactory identification abnormalities seems to extend to structural abnormalities in the underlying neurobiology of the olfactory system. Furthermore, smell identification deficits are also documented in first-episode patients and non-psychotic first-degree relatives of schizophrenic patients. Family members of schizophrenia patients also show structural abnormalities of the olfactory system, suggesting that these may serve as an endophenotype for the development of schizophrenia.

F205. OLFACTORY IDENTIFICATION IN 7-YEAR OLD CHILDREN AT FAMILIAL RISK TO DEVELOP SCHIZOPHRENIA

Anna Hester Ver Loren van Themaat1,2, Jens Richard Mollegaard Jepsen1,2, Camilla Christiani3, Merete Nordentoft4
1University of Copenhagen; 2Mental Health Services – Capital Region of Denmark, Child and Adolescent Mental Health Centre, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research; 3Mental Health Centre Copenhagen

Background: Olfactory dysfunction has repeatedly been observed in individuals diagnosed with schizophrenia. The most stable and consistent finding on the behavioral level is that of smell identification deficits. However, the nature of olfactory identification abnormalities seems to extend to structural abnormalities in the underlying neurobiology of the olfactory system. Furthermore, smell identification deficits are also documented in first-episode patients and non-psychotic first-degree relatives of schizophrenic patients. Family members of schizophrenia patients also show structural abnormalities of the olfactory system, suggesting that these may serve as an endophenotype for the development of schizophrenia.