

T188. MASSIVE OPEN ONLINE DISCOVERY 'MOOD' FOR SCHIZOPHRENIA RESEARCH

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Background: We have recently presented Schizophrenia Interactome, i.e., the network of protein-protein interactions (PPIs) of schizophrenia associated genes. PPIs predicted by our High-precision Protein-Protein Interaction Prediction model (HiPPIP) which uses machine learning to classify features of protein-pairs such as colocalization, coexpression, common molecular functions and biological processes could explain the apparent discordance between modern and historical genetic basis of Schizophrenia (published in npj Schizophrenia), and also were instrumental in discovering that OASL interacts DDX58 to activate the RIG-I immunity pathway during viral infection. These novel predicted PPIs were found to be highly accurate based on computational and experimental validations, and gave insights into possible functions of SZ genes that previously had no-known functional information. Even a single novel PPI can have enormous impact on advancement of biology, when translated effectively. How can we ensure that 500+ of these novel PPIs of schizophrenia interactome are translated effectively?

Methods: We developed a platform for Massive Open Online Discovery for Schizophrenia Research, or "MOOD for Schizophrenia Research", that brings together trained biologists and bioinformaticians including those who are currently not affiliated with research labs (non-research students, PhDs who gave up science careers for administrative/corporate jobs or to take care of families, etc), as well as scientists who are active researchers, to hypothesize, discuss and prioritize the novel PPIs. Hypotheses are written as nano-publications with authorship credit. We are developing a number of features on the portal that allow and encourage scientists to create knowledge around the predicted PPIs and be recognized and given credit.

Results: The first version of our website that disseminates the Schizophrenia Interactome is receiving hundreds of unique users each month. We have since developed MOOD for Schizophrenia Research and will present the key features of the website in this work. Each PPI can be viewed, researched on and written about, by participating scientists. Comprehensive information about the proteins in the PPI regarding their known functions, pathways, diseases and drug associations, is made readily available to scientists, allowing them to hypothesize the importance of the specific PPI. We present methods that we employ to promote collaboration in this work. Initially, the portal starts with a few members and it grows through referral webs (i.e. current members invite new members). The portal has a number of features that recognize and thus entice users to participate. We will also present the user feedback and participation.

Discussion: PPIs are central to cellular systems. Yet less than 10% of estimated PPIs are known today. Thus, the computationally predicted PPIs which are deemed accurate, can accelerate advancement of schizophrenia biology research. The time is ripe to benefit from computer science and information technologies methods for not only discovering aspects of computational biology but to create new mechanisms to promote online collaboration to achieve big things as a summation of nanocontributions. The knowledge potential generated through this system would aid various principal investigators in well established (but ill funded) research labs by giving them access to bioinformaticians and biologists around the world who are eager to be recognized for their contributions. We present here, not merely a website but a novel approach to promote collaborative research between people with heterogeneous skills and commitments by benefiting from the untapped talent of researchers around the world.

T189. PEPTIDE SHARING BETWEEN SCHIZOPHRENIA-RELATED PROTEINS AND THE INFLUENZA A VIRUS MAY OFFER A WINDOW INTO THE IMMUNE AETIOLOGY OF PSYCHOTIC DISORDERS

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Background: Schizophrenia is a complex disorder in which infection and immune mechanisms are thought to play a role. Epidemiological and ecological studies have implicated influenza infection in particular and it is possible that cross-reactivity, or molecular mimicry, between the influenza virus and brain proteins underlies this association. Proteins might share amino acid sequences, which could thus provide the basis for an autoimmune response that targets endogenous proteins. This study is the first to characterise sequence alignment between schizophrenia-related brain proteins and the proteome of the influenza A virus, and comparing it with sequence alignment in proteins not implicated in schizophrenia.

Methods: The software Peptide Match Service (<https://research.bioinformatics.udel.edu/peptidematch/index.jsp>; Protein Information Resource, University of Delaware and Georgetown University Medical Center) was used to obtain sequence alignments between protein sequences. A case-control study design was used to compare schizophrenia-related proteins to proteins not involved in schizophrenia. Schizophrenia-related proteins were operationalised as proteins found significant in the Psychiatric Genomics Consortium schizophrenia genome-wide association studies (GWAS). The control group consisted of null proteins (p-value > .75) in the GWAS. Null proteins were also selected to represent genes expressed in tissues other than central nervous system tissues. Both groups were equalised for the total amino acid count. Perfect pentapeptide matches (i.e. 5 amino acids) in proteins and the influenza proteome were explored.

Results: There was a link between schizophrenia-related (GWAS-significant) proteins and presence of perfect matches between proteins and the influenza proteins polymerase acidic protein ($\chi^2(1) = 5.284, p = .022$, two-sided) and RNA-directed RNA polymerase catalytic subunit ($\chi^2(1) = 6.132, p = .013$, two-sided). Pentapeptide-sharing was found to be highly significant between schizophrenia-related proteins and the hemagglutinin precursor ($\chi^2(1) = 17.723, p = .000026$, two-sided). There was no significant difference ($p > .05$) between schizophrenia-related proteins and proteins not implicated in schizophrenia (GWAS-null proteins) in the frequency of proteins having perfect matches with the influenza A proteins PB2-S1, polymerase basic protein 2, matrix protein 1 and 2, and neuraminidase. However, the result for matrix protein 1 approached statistical significance ($\chi^2(1) = 3.319, p = .068$, two-sided).

Discussion: We find evidence to suggest there is significant overlap between the linear structures of proteins involved in schizophrenia and those integral to the influenza virus. Future research should establish the biological relevance of this finding, particularly regarding the antigenicity of the peptide sequences which we have identified. Extra studies should also go beyond sequences and address structural homologies. Future research could assess whether an immune reaction against particular schizophrenia-related proteins is a plausible mechanism contributing to psychotic disorders. Also, exploring peptide sharing in different influenza strains could offer insights into links between influenza pandemics, maternal infection, and psychosis. Elucidating peptide sharing might have implications for schizophrenia risk management and safe influenza prevention.

T190. ASSOCIATION OF THE HUMAN MU-OPIOID RECEPTOR GENE POLYMORPHISM ASN40ASP WITH SCHIZOPHRENIA

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Background: In humans, opioidergic neurotransmission appears to modulate a variety of behaviors, including the stress response and cognitive processes, as well as anxiety and psychosis. One neurobiological process which may be modified by the Asn40Asp polymorphism of the μ opioid

receptor is the HPA axis response to stress. Hypothalamic corticotropin-releasing hormone (CRH) neurons, which affects glucocorticoid release by stimulating pituitary adrenocorticotropin (ACTH) secretion, are directly and indirectly inhibited by β -endorphin-producing neurons via the μ opioid receptor (OPRM). Both exaggerated and blunted HPA responses to stress have been associated with high risk for psychosis. Many studies have suggested that opioids play an important role in response to stress, motivation, and numerous psychiatric entities. The present association study tested the hypothesis that the Asn40Asp substitution polymorphism confers susceptibility to schizophrenia.

Methods: After informed consent was obtained, 100 schizophrenia patients and 100 control subjects were enrolled in this study. Genomic DNAs were extracted from peripheral blood by using the modified SDS/Proteinase K procedure. The genotypes of the Asn40Asp polymorphism of the μ opioid receptor were assessed by allele-specific polymerase - chain reaction. The PCR products were digested by restricted enzyme.

Results: The frequency of the Asp40 allele was significantly increased in all schizophrenia patients (Fisher's Exact Test $P=0.0118$). There were no associations the Asn40Asp polymorphism of the μ opioid receptor with substance dependence among schizophrenia patients and normal control.

Discussion: The opioidergic neurotransmitter system plays an important role in regulating activation of the hypothalamic-pituitary-adrenal (HPA) axis. Initial activation of the HPA axis occurs at the level of the paraventricular nucleus of the hypothalamus, where neurons that produce corticotropin releasing factor (CRF) are located [Bell et al., 1998]. CRF neurons in this area express μ -opioid receptors and are under tonic inhibition by neurons of the arcuate nucleus that contains β -endorphin [Wand et al., 1998]. Genetic factors appear to be important modulators of HPA axis activation. The HPA axis appears to be involved, including the normal stress response [Bond et al., 1998; LaForge et al., 2000] and psychosis in which HPA axis dynamics appear to be abnormal. Similarly, there is growing evidence that altered opioidergic neurotransmission and HPA axis dynamics may affect alcohol- and drug-seeking behaviors [Piazza and Le Moal, 1997; Kreek and Koob, 1998].

T191. RANDOMIZED DOUBLE-BLIND FEASIBILITY STUDY OF A GLUTEN-FREE DIET IN PEOPLE WITH SCHIZOPHRENIA AND ELEVATED ANTIGLIADIN ANTIBODIES (AGA IGG)

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Background: Deconstructing schizophrenia is important, since different disorders within the syndrome may have distinct pathophysiological mechanisms and treatment targets. Emerging evidence suggests inflammation may play a role in at least a subgroup of people with this illness. One specific subgroup with known inflammation is a group with elevations in antigliadin antibodies (AGA IgG). These elevations (>20 U) are found in about 1/3 of people with schizophrenia. Gliadin is a protein found in wheat, barley and rye. This subgroup with AGA IgG elevations may be distinct as they have fewer positive symptoms, higher kynurenic acid levels, and may benefit from a gluten free diet. The effectiveness of gluten removal has been controversial with mixed results in previous studies, however no former study has examined gluten removal in those with high AGA IgG, that is, the population who may be expected to benefit.

Methods: Sixteen people with a DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder and who also had elevated AGA IgG (≥ 20 U) were recruited and admitted to an inpatient unit for a 5-week randomized double

blind trial. Participants were randomized in a double blind fashion to either a diet containing gluten or a complete strictly enforced gluten free diet. This was accomplished by given 10 gm of gluten flour or 10 gm of rice flour daily in a protein shake, with all meals for all participants being standardized and gluten free. Participants had cooking classes, received cookbooks, and went on shopping trips for gluten free foods and meals. Participants were rated on the Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms (SANS) and the MATRICS Cognitive Battery (MCCB) at baseline and 5 weeks. The study was not powered to find a treatment effect, but designed to examine the feasibility of conducting an inpatient gluten removal study and examine trends in treatment as measured by Cohen's D effect size (ES) differences.

Results: Fourteen of 16 people completed the 5-week trial and all tolerated the diet (2 discontinued early in the trial for housing and administrative reasons). The mean age of participants was 37.9 ± 13.2 years, 56% male and 75% African-American. During the clinical trial, participants receiving the gluten free diet had an improvement in negative symptoms as compared to placebo (treatment difference) with an $ES=0.53$. There was no improvement in BPRS total score or positive symptoms. The MCCB composite score did not improve, but an $ES=0.6$ was noted in the domain of attention favoring the gluten free diet. The AGA IgG levels decreased by 35% in the five weeks in the gluten free diet group relative to a 17% decrease in the gluten containing group. It is also important to note that the correlation between the change in SANS total score and AGA IgG in the gluten free group ($r=0.57$) was strong and notably different than the correlation between the change in SANS total score and AGA IgG in the gluten containing group ($r=-0.017$), suggesting a possible marker of treatment effect. Adverse effects were similar between treatment groups.

Discussion: This is the very first study of a gluten free diet in schizophrenia with elevated AGA IgG. This feasibility study suggests that removal of gluten is associated with improvement in negative symptoms and attention, but not positive symptoms. Participants tolerated the diet. The feasibility study provided data to design the now ongoing fully powered confirmatory double-blind trial in people with schizophrenia with negative symptoms using a higher gluten amount (30 grams daily) and with aims to examine associated mechanisms, with targets of inflammation, neuroimaging and gut permeability.

T192. THE GUT MICROBIOME IN SCHIZOPHRENIA AND ANTIPSYCHOTIC INDUCED METABOLIC DYSFUNCTION

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Background: Antipsychotic (AP) medications are the cornerstone of treatment for schizophrenia (SCZ), with off-label prescription rapidly increasing in youth and adolescent populations. However, APs have been associated with metabolic side effects including diabetes and obesity. Although several mechanisms have been proposed, the gut microbiome (GMB) has been suggested as a potential mediator of AP-induced metabolic side effects due to its role in weight and metabolic regulation; as well as emerging evidence demonstrating a shift in the microbiome of AP-treated animals and humans. The purpose of the current study is to 1) Investigate the GMB in SCZ patients compared to healthy individuals and 2) To examine the role of GMB in SCZ and AP-induced metabolic side effects.

Methods: Three groups of 25 participants are being recruited. Group A: Long-term AP-treated patients (for at least 6 months) taking clozapine (CLZ). Group B: Healthy controls matched with Group A for BMI, age, sex, and smoking status. Group C: Treatment-naive SCZ patients