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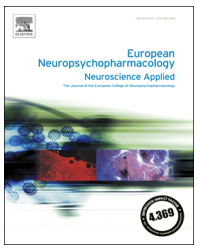

Abstracts of the XXIV World Congress of Psychiatric Genetics (WCPG): 1 November 2016

Tuesday, November 1, 2016
08:30 - 09:30
Plenary Session

DNA METHYLATION: BRIDGING THE GAP BETWEEN GENES AND FUNCTION

Howard Cedar

The Hebrew University of Jerusalem

The human genome contains all of the information needed for constructing every part of the body and for ensuring proper function. In addition to the basic sequence text, there is also a system of gene annotation which instructs cells when and how to use this information and this epigenetic control is usually mediated by DNA methylation. In order to decipher this process, we have studied how methylation patterns are established and maintained during development and deciphered how this influences gene function both in health and in diseases such as cancer. New experiments are beginning to reveal how DNA methylation may play a role in mediating changes in cell function as a result of environmental factors and this is opening up new vistas in our understanding of how the body adapts to its surroundings.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.487

10:00 - 11:15 ISPG Awardee Presentations

BIG DATA IN PSYCHIATRY: GENETICS, GENOMICS, AND BEYOND

Menachem Fromer

Verily Life Sciences

In recent years, large-scale genome-wide association studies (GWAS) of both common and rare variants in neuropsychiatry have yielded specific genetic factors reproducibly associated with disease risk. These molecular findings implicate individual genes and/or larger biological pathways, based on studies of rare (and *de novo*) copy number and single-nucleotide variants, as well as common polymorphic variants.

However, these studies have also made it clear that, as currently defined, neuropsychiatric diseases are truly complex, with observed phenomena of genetic heterogeneity (allelic and/or locus heterogeneity) and polygenicity. Taken together with the observed pleiotropy, this implies that a many-to-many model is required to map genetic risks to disease. These results also suggest that it may be more useful for both diagnosis and treatment to describe disease manifestation in multiple dimensions rather than by classical disease categories. These dimensions range from individual genes and proteins to molecular networks ("systems biology"), the many cell types in the brain, the various brain regions and their connectivities, higher-level human behaviors and processes, and the dynamics within and between these scales over time. But, discovery and validation of these dimensions will require

large amounts of data, automated measurement techniques, and data analytics that span numerous scales.

In this talk, Dr. Fromer will present a selection of past and ongoing works that have approached neuropsychiatric diseases at these various scales of resolution and provide some context of the potential challenges of generating, managing, and analyzing the large datasets required.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.488

11:15 – 13:15 Poster Session II

T1. PREDICTING NON-CODING VARIANT IMPACT ON THE HUMAN BRAIN USING MULTI-OMICS DATA INTEGRATION

Ethan Bahl, Kevin Vervier, Jacob Michaelson

The University of Iowa

Background: Recent studies show evidence that non-coding variants may play an important role in disease etiology, including psychiatric disorders. However, prioritizing these less-understood variants and selecting the right candidates for further investigation remains a central challenge in the field. Current tools for annotating non-coding genetic variations provide a general indicator of their deleteriousness, but lack, for example, tissue-specific context that could better illuminate their role in a particular disease.
Methods: In this work, we propose a new machine learning-based approach that relies on tissue-specific data to estimate variant impact on brain tissues. By integrating information from several genome-scale databases, including GTEx and RoadMap Epigenomics, we derive tissue-related features. Using this data representation, we train a predictive random forest model to discriminate variants with prior evidence for brain relevance from variants unlikely to affect the brain. The resulting model predictions, which we call the Brain Relevance Score (BRS), are an estimate of how related a genome position is to the brain.
Results: After computing BRS for every nucleotide position in the human genome, we validate it on genomic regions known to be related to psychiatric disorders, such as the 16p11.2 region. In this region, we identify a short list of candidate variants, close from known genes involved in brain disease and mental disorders. We then use BRS as a filter and combine it with state of the art deleteriousness score (e.g., CADD) and report higher sensitivity in detecting brain-related damaging variants in the Simons Simplex Collection data for autism spectrum disorder, compared to 1000Genomes control data set.
Discussion: Even if we reported high performance in detecting both coding and non-coding variants related to the human brain, ongoing work in our lab involves benchmarking more competitive learning approaches and integrating additional brain databases in the model. The learning framework we demonstrate here could be easily applied to other psychiatric disorders.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.489

T2. IDENTIFICATION OF PATHOGENIC VARIANTS IN PROTEIN CODING GENES

Sahar Gelfman[1], Quanli Wang[2], K Melodi McSweeney[2], Zhong Ren[2], Francesca La Carpia[3], Matt Halvorsen[2], Kelly Schoch[4], Erin L. Heinzen[2], Michael J. Boland[2], Slavé Petrovski[5], David Goldstein[2]

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Background: A central aim of precision medicine is to target treatments to the underlying causes of disease. To accurately target treatments we must be able to recognize pathogenic genetic variants. Current methods prioritize variants that directly alter protein sequence (missense and loss of function) but not variants that may cause disease by changing the processing of final transcripts. The difficulty in capturing this effect results in overlooking synonymous and intronic variants when searching for disease risk in sequenced genomes.
Methods: The TraP score was constructed using three main components: 1) Information acquisition – details of the harboring gene and it's transcripts are gathered for each variant. 2) Feature calculation - possible changes to sequence motifs are evaluated, including changes to exon-intron boundaries, creation of cryptic splice sites, creations and disruptions of cis-acting binding sites for splicing regulatory proteins, interactions between selected features such as original and new splice sites and others. Overall, 42 features and 14 general properties (chromosome, strand, coordinate, etc.) are collected for each variant. 3) Modeling – the incorporation of selected features into a random forest model. The model is trained on a set of 75 pathogenic synonymous variants and 402 benign variants. Pathogenic variants are strongly associated with rare disease, whereas the 402 benign variants are de novo mutations identified from healthy individuals.

Results: The Transcript-inferred Pathogenicity score (TraP) presented here was constructed to reliably identify non-coding mutations that cause disease. Trap is strongly negatively correlated with allele frequency in both synonymous and intronic regions, suggesting that the higher the TraP score the stronger the selection against these variants in the population. Moreover, synonymous variants with high TraP scores have significantly lower minor allele frequencies than even missense variants, indicating that Trap identifies a subset of synonymous variants under stronger purifying selection. TraP identifies known pathogenic variants in synonymous and intronic ClinVar datasets (AUC = 0.88 and 0.83, respectively), dismissing benign variants with extremely high specificity of above 99%. Applied to exomes of 281 epilepsy family trios, TraP pinpoints synonymous de novo variants in known epilepsy genes. TraP's high performance and specificity clearly outperforms existing methods and allows the prioritization of synonymous and intronic variants for use in gene discovery and the interpretation of personal genomes.
Discussion: Exome sequencing studies consider rare non-synonymous variants as disease candidates, while other variant types are mostly ignored. Some existing methods are able to prioritize synonymous and intronic variants, yet lack the specificity required for detection of causal variants. TraP discards over 99% of non-coding variants as benign while strongly identifying true pathogenic variants. TraP identifies pathogenic variants that are not conserved, yet have rare population frequencies. Doing so without prior population frequency information and in contrast to the GERP++ and CADD scores, suggests that TraP identifies pathogenic events that were not selected against during vertebrate evolution, but are selected against in human population. This conclusion is supported by the highest complexity of alternative splicing found in primates and by the species-specific nature of splicing regulation.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.490

T3. EVIDENCE FOR ASSOCIATION OF GENETIC VARIANTS IN PRI-MIR-34B/C AND ABNORMAL MIR-34C EXPRESSION WITH ATTENTION-DEFICIT AND HYPERACTIVITY DISORDER

Iris Garcia[1], Cristina Sánchez-Mora[1], Mireia Pagerols[1], Vanesa Richarte[2], Montse Corrales[2], Christian Fadeuilhe[2], Bru Cormand[3], Miguel Casas[2], Josep Antoni Ramos-Quiroga[2], Marta Ribases[1]

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Background: Attention-Deficit/Hyperactivity Disorder is a prevalent neurodevelopmental disorder characterized by impairment to sustain attention, and inability to control impulses and activity level. The etiology of ADHD is complex, involving genetic and environmental factors, with an estimated heritability of 76%. However, consistent genetic factors with a major role in its susceptibility have not yet been discovered. Growing interest has been addressed to genetic variation in epigenetic mechanisms, especially regarding miRNAs, small non-coding RNA molecules which direct mRNA posttranscriptional repression. Here, we attempted to unravel novel susceptibility factors for ADHD by a case-control association study focused on miRNAs and their target genes. Once identified the risk loci, we studied miRNA expression differences in peripheral blood mononuclear cells of ADHD subjects and controls, and tested the effect on expression of the risk SNPs by expression quantitative trait loci (eQTL) analyses.
Methods: We selected tagSNPs in 53 genomic regions containing 134 miRNAs with at least one confirmed target gene involved in ADHD or other psychiatric disorder, and performed a case-control association study considering 754 ADHD adults and 766 healthy sex-matched unrelated controls. Subsequently, differences on expression levels of the encoded miRNAs within these regions were evaluated through Quantitative Real-Time PCR (qRT-PCR) in peripheral blood mononuclear cells (PBMCs) of 31 ADHD subjects and 32 controls. The impact of the risk markers within the associated loci on gene expression was evaluated through analysis eQTL in cis and trans in PBMCs from 45 subjects with ADHD. Top hits from eQTL results were considered for canonical pathway enrichment and gene networks studies.
Results: Five loci were found associated with ADHD: miR-128-2 and let-7a-1/let-7f-1/let-7d, let-7a-3/miR-4763/let-7b, miR-34b/34c and miR-371/372/373 clusters. Only rs28690953 (P=8.8e-04) and the haplotype rs4938723-rs28690953 (P=5.0e-03) in pri-miR-34b/34c surpassed FDR correction. Three miR-34b/34c target genes were also associated with ADHD: rs1621 (P=8.3e-03) and rs6566 (P=0.017) in MET, rs699779 in NOTCH2 (P=7.7e-03) and rs1175982 in HMGA2 (P=7.5e-03). MiR-34c-3p was over-expressed in ADHD subjects (P=6.5e-03; Exp(B)=4.19; CI=1.25-14.05), and miR-34b-3p also showed a trend towards over-expression (P=0.058; Exp(B)=2,70; CI=0.89-8.20). Cis-eQTL analyses revealed an inverse correlation between rs4938723T risk allele dosage in the promoter of pri-miR-34b/34c and expression levels of miR-34b-3p (P=0.021, Beta=-0.41) and miR-34c-3p (P=0.027, Beta=-0.44). Trans-eQTL analyses considering rs4938723T revealed 681 differentially expressed transcripts.This gene set was enriched for miR-34b/34c binding sites, serotonin biosynthesis and signaling canonical pathways, and other functional categories of the central nervous system.
Discussion: Our results provide preliminary evidence for the contribution to ADHD of a functional variant in the pri-miR-34b/c promoter, possibly through dysregulation of the expression of mature forms of miR-34b and miR-34c and some target genes. These data highlight the importance of abnormal miRNA function as a potential epigenetic mechanism contributing to ADHD.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.491

T4. USING DROSOPHILA TO STUDY THE FUNCTIONALITY OF A CHROMATIN REGULATORY GENE INVOLVED IN ASD

Neta Herman[1], Sagiv Shifman[2], Sebastian Kadener[1], Dana Perez[1]

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[2]*Genetics Department, The Hebrew University of Jerusalem, Israel*

Background: Autism spectrum disorder (ASD) is a heterogeneous genetic syndrome characterized by social deficits, language impairments and repetitive behaviors. We now know that autism could be triggered by different types of genetic variations in different types of genes.

Chromatin regulator genes found to be one of the most enriched group of genes disrupted in ASD. We suggest using Drosophila models for studying the chromatin related genes that are disrupted in ASD.

Recently, several papers studied and found individuals with POGZ de novo disruptive mutations and defined shared phenotypes including developmental delay, vision problems, microcephaly, hyperactivity and tendency to obesity. All this information lead POGZ gene to consider as a high risk ASD and ID gene. POGZ involved in chromatin regulation, binds different isotypes of the human heterochromatin protein 1 (HP1α, HP1β and HP1γ)

To identify orthologs of POGZ in Drosophila we used both a reverse Blast method and treefam database. We identified the gene ROW as the Drosophila ortholog of POGZ. Similar to POGZ, ROW was identified as a binding partner of heterochromatin protein 1, HP1c and HP1B.

Methods: We used flies with knockdown of ROW and cloned the gene into the UAS/GAL4 system in order to establish flies with its overexpression. We examine the behavior of the affected flies and currently the effects of ROW knockdown on transcription and on chromatin state by RNA-seq, MNase-seq and Chip seq in the context of the nervous system. We also aim to perform Co-IP experiment in order to find ROW's binding partner in the nervous system.

Results: We show that once the efficiency of the knockdown in the protein level is highly significant, those flies show partial lethality, shorter life span, fertility and sleeping problems. Moreover, Ubiquitous overexpression of ROW lead to complete lethality of the flies, therefore we used conditional system expressed only in neurons. By analysis of Chip-seq data we show ROW overlaps with histone modifications and proteins associate with transcriptional activation. Therefore, currently we work on examining its effects on transcription and on chromatin state.

Discussion: Here we show our attempts towards establishing a Drosophila model for the POGZ ortholog, ROW. We expect the model to help us characterize the role of ROW in the Drosophila nervous system and understand the functional relevance of POGZ to ASD.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.492

T5. DNA METHYLATION PROFILE OF CORTICAL NEURONS IN AUTISM SPECTRUM DISORDER: SPECIFIC ALTERATIONS IN GABAERGIC AND IMMUNE RESPONSE RELATED GENES

Evan Elliott, Stefano Nardone, Dev Sharan Sams, Eli Reuveni

Bar Ilan University

Background: Autism Spectrum Disorder (ASD) is a neuropsychiatric syndrome with a complex etiology. The potential for non-genetic influence to mediate part of the risk of ASD has prompted several studies to date, all showing evidence for epigenetic alterations in autistic subjects. Establishment of DNA methylation during brain development has been widely accepted as key factor in defining neuron molecular identity. However, one of the most challenging barriers faced in epigenetic studies is the cellular mosaicism in the brain, which can mask the discovery of neuron-specific epigenetic phenotypes. Our study determined the neuron-specific dysregulation of DNA methylation patterns in the brains of individuals diagnosed with ASD.

Methods: In order to unravel the contribution of neuronal population to the entire epigenetic signature in ASD, we employed two techniques: Fluorescent Activated Cell Sorting (FACS) of neuronal nuclei from human postmortem brains, followed by hybridization on 450K Methylation Array (Illumina), that profiles around 485,000 CpG sites throughout the entire genome. Differentially Methylated Regions were determined using the CHAMP bioinformatics package, which runs the bumphunting algorithm. Weighted Gene Coexpression Network Analysis (WGCNA) was performed to identify networks of CpGs whose methyaltion status correlated with the autism phenotype.

Results: We identified 12 Differentially Methylated Regions (DMRs) at FDR <0.01. Interestingly, multiple genes were part of the GABAergic system whose involvement has been strongly implicated in ASD. Weighted Gene Co-Expression Network Analysis (WGCNA) pinpointed three co-methylation modules correlated to autism/control status at p value <0.0001. Two of them were inversely correlated to autism/control status and were enriched for synaptic and neuronal genes, while the third module showed a direct correlation and was enriched for

immune response processes. Finally, we established the specificity of these 3 modules to ASD assessing their enrichment for GWAS databases related to other psychiatric and non-psychiatric disorders.

Discussion: This study identifies alterations of DNA methylation in cortical neurons as a possible factor involved in the aetiop athogenesis of ASD. We have identified epigenetic dysregulation in the GABAergic system in cortical neurons of individuals with ASD. Multiple previous studies have determined a dysfunction of GABAergic signaling in the autism brain, and our study suggests that this may have an epigenetic origin. In addition, our study determined a dysregulation of genes involved in the immune response, including complement factors. Considering that many of these same genes have important roles in neuronal development, this suggests an interaction between immune response, epigenetics, and neuronal development. This current study also promotes a more systematic use of cell-specific approaches in psychiatric epigenetics.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.493

T6. AN INVESTIGATION OF ASSORTATIVE MATING PATTERNS AND UNDERLYING GENETIC CORRELATES IN PARENTS OF OFFSPRING WITH ASD

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Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder with a complex genetic etiology. Little is known about the role of inherited common variants in the development of ASD and it's persistent, and perhaps increased, frequency in our population, despite decreased fecundity in ASD individuals. One possible explanation for this phenomenon is assortative mating. Individuals with elevated, but sub-diagnostic ASD behaviors may be more likely than chance to mate, and thus increase the likelihood of their offspring of inheriting an underlying genetic load that pushes them over the ASD diagnostic threshold. In parents of children with ASD, we investigate 1) If genetic risk for ASD, schizophrenia (SCZ) or height can predict ASD-like behaviors 2) If they are more similar than chance in their ASD-like behaviors and their genetic risk for ASD, SCZ or height and 3) If there is a correlation between ASD behavioral and genetic similarity.

Methods: Analyses were performed on 2727 Caucasian parental pairs of children with ASD in the Simons Simplex Collection. All parents completed the Broad Autism Phenotype Questionnaire (BAPQ) and were genotyped via microarray. After standard quality control measures, Polygenic Risk Scores (PRS) were calculated in PLINK using summary data from published GWAS for SCZ, ASD, and height. Linear regression was performed in R to predict individual PRS based on individual BAPQ scores for all phenotypes. Degree of correlation between mothers and fathers was calculated for both BAPQ scores and PRS for SCZ, ASD, and height. Finally, the degree of correlation was calculated between the squared difference of mother and father BAPQ scores and the squared difference between mother and father PRS for all phenotypes.

Results: For parents of children with ASD, individual PRS for ASD, SCZ or height did not predict individual BAPQ total or subscale scores ($b = -0.06$ – 0.3 , $p > 0.01$). Total BAPQ score and BAPQ pragmatic subscale scores were strongly correlated between parents ($r = 0.14$, $p = 1.4e-12$; $r = 0.11$, $p = 2.4e-8$). PRS for both ASD and SCZ were also strongly correlated between parents ($r = 0.16$, $p = 1.1e-9$; $r = 0.19$, $p = 3.9e-14$). Height PRS were more weakly correlated ($r = 0.08$, $p = 0.003$). Squared difference of parental PRS scores for all phenotypes were not predictive of the squared difference of parental total BAPQ scores or any subscales ($b = -0.07$ – 0.02, $p \geq 0.01$).

Discussion: Assortative mating is an established phenomenon in individuals with ASD. Here, we show that parents of individuals with ASD are also more likely than chance to highly correlate on broad autism phenotype measures, primarily on pragmatic language measures. Pragmatic language measures are, for example, when someone says inappropriate or unrelated things during conversations or has little variety in language use. Further, we found that parents of children with ASD have highly correlated PRS for both ASD and SCZ, but not height (our non-psychiatric control phenotype). Therefore, we hypothesized that the degree of correlation between ASD and SCZ genetic risk may predict correlation on total BAPQ measures or on the BAPQ pragmatic language subscale. However, the results of this analysis found that there was no significant correlation between these measures. This suggests that the genetic similarity we captured through PRS may reflect assortative mating in parents of ASD individuals due to factors other than autistic-like behaviors and that there are yet unknown factors underlying BAPQ similarities between parents of ASD individuals.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.494

T7. CNS PATTERNING GENE VARIANTS MAY BRIDGE THE GAP BETWEEN AUTISTIC SYMPTOMS AND BRAIN CORTICAL STRUCTURE

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Background: Abnormal cortical anatomy has been identified as a significant feature of the neuropathology of autism spectrum disorders (ASD). The CNS patterning gene, the wingless-type MMTV integration site family, member 2 (WNT2), has been shown to be associated with the risk for ASD and is essential for promoting cortical dendrite growth and dendritic spin formation. Whether the WNT2 variants are associated with clinical severity of autistic symptoms and cortical development is not yet studied. This study aims to investigate the genetic association between WNT2 variants and (1) clinical severity of ASD, and (2) the cortical thickness in individuals with ASD and typically-developing controls (TDC).
Methods: The genetic association study recruited 391 patients (males, 88.3%; mean age ± SD, 9.5 ± 4.4 years) diagnosed with ASD. Six tagging SNPs of WNT2 were genotyped and analyzed by their genetic association with the core symptoms of ASD. The candidate SNPs were selected for each linkage disequilibrium block across 5'-UTR to 3'-UTR. The neuroimage study included 122 patients with ASD (males, 95.8%; mean age 13.1 ± 6.4 years) and 118 TDC (males, 61.5%; man age 21.0 ± 9.7). Cortical thickness on MRI was analyzed by FreeSurfer software with 74 automatic parcellation. The main effect of each SNP and group*SNP interaction were examined for each region.
Results: In genetic association study, we found that the multi-locus markers of WNT2 were associated with communication problems and restricted/stereotyped behaviors in ASD. Patients who carry a specific haplotype showed more severe symptoms. In neuroimage study, we found that mean cortical thickness as well as nine cortical regions were reduced in ASD compared to TDC in a subsample with compatible sex and age (88 ASD and 51 TDC, mean age 13 years). Meanwhile, the WNT2 variants showed a main effect and an age interaction on the mean cortical thickness of bilateral hemispheres, as well as several brain regions including cingulate cortex and superior temporal cortex.
Discussion: In conclusion, our findings suggest that the variants of CNS patterning gene WNT2 may play a role in modulate the clinical severity and neuroimage phenotypes of ASD. Patients who carry specific WNT2 variants showed more severe communication deficits and severe stereotyped behaviors. Besides, WNT2 variants might contribute to the reduced cortical thickness found in ASD; subjects who carry specific genotype may experience accelerated cortical thinning during adolescence and early adulthood. These findings may be worth validation and further investigation.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.495

T8. GLUTAMATERGIC SIGNALLING AND AUTISM: A FAMILY BASED ASSOCIATION STUDY ON THE GLUTAMATERGIC NEUROTRANSMITTER SYSTEM

Christine M. Freitag[1], Afsheen Yousaf[1], Hannah Bour[1], Denise Haslinger[1], Eftichia Duketis[1], Tomasz Jarczok[1], Michael Sachse[1], Anette Voran[2], Monika Biscaldi-Schäfer[3], Stefan Kupferschmid[4], Michael Schulte-Rüther[5], Franziska Degenhard[6], Stefan Herms[6], Sven Cichon[7], Ina Koch[1], Ric Anney[8], Andreas Chiocchetti[1]

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Background: Common single nucleotide polymorphisms (SNPs) explain around 50% of genetic risk underlying Autism-Spectrum-Disorder (ASD). In a previous study we showed that common functional SNPs of genes implicated in Fragile X Syndrome (FXS) were associated with ASD (Waltes et al., 2014). The FXS associated protein FMRP is regulated by the glutamatergic system, a patho-mechanism discussed for ASD.
Objective: We tested if functional common SNPs of glutamatergic genes were associated with ASD or ASD specific symptoms in two large ASD family cohorts (Autism Genome Project/AGP set, N=2734 families; German data set N=578 families). Since the genetic architecture between individuals with High IQ (HIQ= IQ>70) and Low IQ (LIQ= IQ≤70) differs (Vieland et al., 2010), we also split the two cohorts into high and low functioning (HIQ, LIQ) individuals.
Methods: 207 functional SNPs of 124 glutamatergic genes with a minor allele frequency over 5% were tested using Plink v 1.9 (DFAM) in the cohort with HIQ, LIQ and the combined cohorts, respectively. Phenotype association was studied by logistic ordinal regression correcting for gender, IQ, clinical site and population stratification. Phenotype measures were taken from the Autism Diagnostic Interview-Revised (ADI-R) scores for Social Interaction (Domain A), Verbal Communication (B1-B4; verbal individuals only), Non-Verbal Communication (Domain B2; B3; all individuals) and Repetitive Behavior (Domain C). Variants significant in both cohorts with effect sizes in the same direction were considered as replicated. Similarly, genes with any nominal significant variant in both cohorts were considered as replicated hits.

Results: We identified nominal significant associations of variants rs7206796 and rs3790112 (GNAO1) as well as rs3742926 (AKAP6) in both the German and the AGP LIQ cohort. In addition, significant but not overlapping SNPs of AKAP2 were identified (LIQ only). rs731826 (AKT1S1) was associated with Non Verbal Communication in the HIQ cohorts. In addition, we report 24 variants that were nominally associated with ADI-R scores in both cohorts. Genes that were involved in all five phenotypes tested were strongly related to the mTOR Pathway (e.g. genes MTOR and TSC2) or the second messenger system (e.g. G-proteins GNAS, phospholipases PLCB, protein phosphatases PPP1CA). A subset of genes was specific to each phenotype or significant in one of the subgroups (HIQ and LIQ) only. For example AKAP13 or RPS6K are associated with Verbal Communication in Low Functioning Individuals.

Discussion: Replication and extending previous findings we found that variants of genes that are associated with glutamate signaling, and specifically the mTOR pathway are modulators of ASD symptoms. Genes such as TSC1 or RPS6K are known to mediate glutamatergic signaling through mTOR, whereas AKAP proteins are important interactors of glutamate receptors (Sanderson et al., 2011). Both, the mTOR pathways and AKAP proteins have previously been associated with ASD (Chen et al ., 2014; Poelmans et al., 2013). Further functional analyses of glutamatergic variants are thus recommended to elucidate ASD etiology.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.496

T9. COMBINING AUTISM AND INTELLECTUAL DISABILITY EXOME DATA IMPLICATES DISRUPTION OF NEOCORTICAL DEVELOPMENT IN BOTH DISORDERS

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Background: Autism spectrum disorder (ASD) and intellectual disability (ID) are known to be highly co-morbid, but whether their genetic risk converges on a common neurodevelopmental process is unknown. Integrative approaches using genetic evidence and brain co-expression data have proven useful in pinpointing specific developmental epochs and, within them, discrete neural circuits where risk for ASD maps. These analyses have shown that the strongest signal occurred in the neocortex, specifically in the prefrontal cortex and primary motor-somatosensory cortex (PFC), during mid-fetal development. However, it is unknown how ASD and ID risk intersect at this critical spatio-temporal window for neurodevelopment. These findings motivate a genetic analysis that contrasts and combines discoveries and leverage genetic evidence to shed light on the neurobiology underlying shared risk.

Methods: We used a statistical method called TADA (Transmission And De novo Association) to identify likely risk genes in ASD, ID and both disorders in 4,216 ASD and 1,479 ID families, as well as 869 ASD cases and 2,829 ancestry-matched controls. We integrated the genetic scores derived from the TADA analyses in ASD with the gene co-expression data from the BrainSpan mid-fetal PFC. The resulting DAWN network was evaluated to identify tightly integrated, functionally-related gene communities. We also conducted an analysis of single-cell RNA-sequencing data from single cells laser-microdissected from human neocortex specimens at 12 and 13 weeks post-conception (apical progenitors in the ventricular zone, subventricular basal progenitors, and neurons in the cortical plate).

Results: Using TADA, we defined genes associated with risk for ASD and ID (referred to as tASD, tID to denote TADA-implicated genes). Within the DAWN network built on the TADA scores in ASD and gene co-expression in the mid-fetal PFC, we identified two functionally related gene communities: the 'chromatin modification' and the 'transcription factor' community. Both communities were significantly enriched for tID genes, with the 'chromatin modification' community having the strongest enrichment. Notably, many of the transcription factors connected in the community belong to tightly regulated cascades that control the specification of laminar fate identity in progenitors and neurons. Protein-protein interaction analyses corroborated these conclusions, with two linked modules related to synaptic transmission, and another two related to chromatin modification.

Within this critical spatio-temporal nexus for risk, apical (ap) and basal progenitors (bp), and neurons (n) are all strongly expressing for tASD genes, with a steady increase in the enrichment from types ap to bp to n. A milder and more symmetrically distributed enrichment was observed for tID genes.

Discussion: Our analyses of gene expression of mid-fetal neocortical cells and tissue-level co-expression implicate developmental disruption of cortical projection neurons in the etiology of both ASD and ID. Our analyses suggest that mutations in ASD risk genes prominently affect processes relevant to postmitotic neurons, while ID risk might extend to processes preceding acquisition of neuronal differentiation. Within these developmental frames, chromatin remodeling and transcriptional networks were reaffirmed as prominent pathways in both ASD and ID.

Disclosure

Nothing to Disclose.

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T10. ALZHEIMER'S DISEASE AND NEUROTRANSMISSION GENE VARIANTS

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Background: Alzheimer disease (AD) is a chronic neurodegenerative disorder that accounts for 60% to 70% of cases of dementia. The 49% to 79% of the disease risk has been associated with the genetic background of the individuals. Two main forms of AD have been recognized: the early-Onset AD (EOAD) and the late-onset AD (LOAD). The EOAD genetic background shows an autosomal dominant mode of inheritance and is strongly related to variations within amyloid b precursor protein, presenilin 1 and presenilin 2. However, it accounts for no more than 5% of the cases of AD. The remaining part of AD cases are categorized as LOAD, which shows a multigenic inheritance. In the last years, great importance has been attributed to the gene coding for apolipoprotein E. However, other factors must be involved in the development of AD. For this reason, in the last decades, a number of other genes have been investigated. Among them, an increasing interest is accumulating in the genes involved in the molecular mechanics of neurotransmission. The aim of the present paper is to focus on some genes involved in this process.
Methods: The samples were recruited in two independent centers, one in Athens (Greece) and one in Emilia Romagna (Italy), for a total of 156 AD subjects and 301 healthy controls. Two sets of genes were investigated for association with AD in two independent samples. The first set includes genes involved in key points of the neurotransmission mechanisms (COMT, PPP3CC, HTR2A), while the second set includes a group of genes associated with important processes like memory learning and synaptic plasticity (SIRT1), synapses function (SORBS3), circadian function and serotonin levels balancing (RORA) and modulation of neurotransmitters release (SIGMAR1). A total of 16 SNPs within the above genes were investigated. Exploratory analyses on psychosis and depression comorbidities were also performed, as well as on other clinical and serological parameters available in the Greek sub-sample only. Analysis of variance, of co-variance and chi-square statistical analyses were performed. The samples were tested for genotype and alleles. According to Bonferroni's formula, the α value for the primary analyses was set at $\alpha=0.003$.
Results: AD was associated with rs4680 within COMT gene in the total sample, while trends of association were found in the two sub-samples as well. No relation with psychosis was found for the SNPs investigated. On the other hand, some nominal associations were found concerning depression phenotype. In particular, rs1099781 and rs10997875 within SIRT1 were nominally associated with depression in the total sample as well as in the Greek sub-sample. Rs174696 within COMT was instead associated with depressive symptomatology in the Italian sub-sample only.
Discussion: Our data further support the role of COMT, and particularly rs4680, in the pathogenesis of AD, while SIRT1 seems to modulate the depressive symptomatology in this population. Clearly, further studies are required to confirm our preliminarily results.

Disclosure

Nothing to Disclose.

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T11. REPLICATIVE ANALYSIS OF 30 SNPS IN RUSSIAN PATIENTS WITH ALZHEIMER'S DISEASE

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Background: Alzheimer's disease is a highly heritable genetically heterogeneous disorder with 60%–80% of risk attributed to genetic factors. Two forms of the disease are known as Early-onset familial Alzheimer's disease and Late-onset sporadic Alzheimer's disease. Although scientists know how brain cells of persons with Alzheimer's disease are affected, and additionally understand some of the genetic explanations of the disease, the precise cause of this disease is still unclear. There are over 90 Genome-Wide Association Studies for Alzheimer's disease. However, only a few associations were replicated in independent data. The aim of this study was to analyze associations of 30 SNPs reported in GWAS with Alzheimer's disease in Russian population of Siberian region.
Methods: 108 patients with AD and 285 healthy controls, matched to the patients by age, gender, and ethnicity were included in this study. 30 SNPs were genotyped by MALDI-TOF mass-spectrometry using MassARRAY Analyzer 4 (Sequenom). Allele-specific ORs and associated p-values were calculated.

Results: We found three significant associations of SNPs with AD in Russian patients of Siberian region: rs17594526 at TCF4 gene (OR = 1.77, p=0.003), rs11064768 at CCDC60 gene (OR = 2.15, p= 0.02) and rs12922317 at SNX29 gene (OR = 1.47, p= 0.02). These genetic markers were previously reported in GWAS associated with schizophrenia.
Discussion: Only the TCF4 gene has known functional importance for cognitive dysfunctions of schizophrenia and Alzheimer's disease. As a transcription factor, the TCF4 gene regulates the expression of other genes involved in cell differentiation, survival, and neurodevelopment. Genetic markers of CCDC60 and SNX29 are associated with Alzheimer's disease but their role in pathogenesis of the disease is not clear. This work was supported by the Russian Science Foundation (project # 16-14-00020).

Disclosure

Nothing to Disclose.

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T12. THE LIPIDOME IN MAJOR DEPRESSIVE DISORDER: SHARED GENETIC INFLUENCE FOR ETHER-PHOSPHATIDYLCHOLINES, A PLASMA-BASED PHENOTYPE RELATED TO INFLAMMATION, AND DISEASE RISK

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Background: The lipidome is rapidly garnering interest in the field of psychiatry. Recent studies have implicated lipidomic changes across numerous psychiatric disorders, not least in MDD—there is growing evidence that the concentrations of several classes of lipids are altered in those diagnosed with MDD. However, for lipidomic abnormalities to be considered potential treatment targets for MDD (rather than secondary manifestations of the disease), a shared etiology between lipid concentrations and MDD risk must be demonstrated.
Methods: In a sample of 567 individuals from 37 extended pedigrees (average size 13.57 people, range = 3-80) plus 30 singletons, we used mass-spectrometry lipidomic measures to evaluate the genetic overlap between twenty-three biologically distinct lipid classes and a continuous index of lifetime MDD risk.
Results: We found that the lipid class with the largest endophenotype ranking value (ERV, a standardized parametric measure of pleiotropy) were ether-phosphodatidylcholines (alkylphosphatidylcholine, PC(O) and alkenylphosphatidylcholine, PC(P) subclasses). Furthermore, we examined the cluster structure of the twenty-five species within the top-ranked lipid class, and the relationship of those clusters with MDD risk. This analysis revealed that species containing arachidonic acid generally exhibited the greatest degree of genetic overlap with MDD.
Discussion: This study is the first to demonstrate a shared genetic etiology between MDD risk and ether-phosphatidylcholine species containing arachidonic acid, an omega-6 fatty acid that is a precursor to inflammatory mediators, such as prostaglandins. The study highlights the potential utility of the well-characterized linoleic/arachidonic acid inflammation pathway as a diagnostic marker and/or treatment target for MDD.

Disclosure

Nothing to Disclose.

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T13. GWAS OF BSNIP BIOFACTORS AND BIOTYPES AS INTERMEDIATE PHENOTYPES FOR PSYCHOSIS

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Background: The Bipolar and Schizophrenia Network of Intermediate Phenotypes (BSNIP) is an ongoing NIMH-funded study aimed to identify biomarker-based classification of psychoses, with clinical, imaging and neurophysiological phenotypes, consistent with Research Domain Criteria. Analyses of the first BSNIP cohort (BSNIP1) reported 3 categorical Biotypes of patients derived from cluster analysis of 9 PCA-derived integrated measures of cognitive and neurophysiological experimental paradigms (Clementz,

B. et al., Am J Psychiatry 173:4, April 2016). In the present work we ran Genome-Wide Association Studies using these Biotypes as phenotypes.

Methods: 711 Cases and 460 Control unrelated individuals from the BSNIP1 study were genotyped using the Illumina PsychChip followed by imputation using the 1000Genomes reference panel. 4,322,238 imputed SNP markers were included in GWAS using PLINK regression analysis, controlling for ethnic background with PCA. Analyses of each of the 3 categorical Biotypes vs. Control were performed, as well as each Biotype against the other two. Finally a GWAS was done using the quantitative scores derived from the paradigms' PCA analysis ("Biofactors").

Results: After Bonferroni correction (α=1.15E-08), there were no significant associations. However we report here some suggestive and possible associations. Analysis of Biotype3 vs. Controls identified SNPs on the Chr.11p11.2 region with P=1.044E-07. GWAS of Biotype1 vs. Biotypes 2 & 3 found a marker on Chr.12q24.22 with P=2.411E-07. Results from quantitative trait analysis of Biofactors identified a SNP in the glutamate ionotropic receptor gene GRIN2B with the lowest P=9.50E-08. GRIN2B was also suggestively associated with the Sensorimotor Reactivity biofactor with a P=2.03E-07. Sensorimotor Reactivity also had a P=1.59E-07 association with the Chromosome 4 open reading frame 22 (C4orf22) located on Chr4q21.21. The Cognitive Control biofactor was suggestively associated with a locus on Chr.3p21.1 (P=1.52E-07).

Discussion: Despite the limited power of the sample size, some of our GWAS identified suggestively related SNPs to data-derived measures of experimental paradigms of psychosis (Biofactors) and distinguished one of the integrated clusters (Biotypes) from controls.

Disclosure

Nothing to Disclose.

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T14. DIGITAL PHENOTYPING IN BIPOLAR DISORDER

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Background: Diagnostic categories of psychiatric illnesses based on subjective clinical assessments have been the standard for phenotyping in genetics studies. This is a significant problem for disorders such as bipolar, wherein the course of the illness is an important element of the phenotype. Digit phenotypes, assessed using mobile devices, offer an objective method of gathering data to describe phenotypes for translational research. It has been established that speech patterns are altered in mood disorders. The challenge is to monitor moods over extended periods of time using speech or other mobile-based methods and technology on personal devices. Technology is likely to be incorporated into the ongoing assessment and monitoring of individuals if it is passive and integrated into daily routines; mobile smartphones are ideal.

Methods: Individuals with rapid cycling bipolar disorder (51) and healthy controls (9) were ascertained from a prospective longitudinal study of bipolar disorder. They were provided with a smartphone pre-loaded with "PRIORI", an app that securely recorded and encrypted all outgoing speech from all telephone calls sent and received. Two android-based phones were used, the Samsung Galaxy S3 and S5. Weekly assessment calls with a clinician included a depression and mania rating scale (HamD) and (YMRS). The encrypted calls were transferred to a central secure server for processing. Pre-processing included a de-clipping algorithm as it was found that the S3 was "clipping" the audio. The audio was segmented and features of rhythm were extracted and support vector machines were used to classify the speech. This presentation focuses on a subset of 217 acoustic features and solely on assessment calls with the clinician.

Results: Initial analyses included 37 individuals with two or more episodes wherein HamD $>$ 10 and YMRS $<$ 6; YMRS $>$ 10 and HamD $<$ 6. The baseline evaluation without the de-clipping pre-processing showed an AUC of 0.64 for depression and 0.57 for mania. The S5 smartphone performed better than the S3. Significant clipping occured in the S3, primarily in the manic calls. When a declipping algorithm was applied in preprocessing, the AUC for mania was 0.70 (both S3 and S5 data combined). The effect of segmentation was studied by analyzing 2 second sub-segments across the whole call, including silences. This approach improved the sensitivity of the system, the AUC for mania was 0.74 and 0.77 for depression.

Discussion: Digital phenotypes derived from speech captured from mobile devices predict mood states. There are many challenges in addressing the comparability of data collected from across devices with different acoustic sensitivity. We demonstrate that through preprocessing, feature extraction, and data modeling techniques it is possible to mitigate the effects of differing amounts of clipping, loudness, and noise. The goal for a digital phenotyping system is to be passive, requiring no active input from the patient or the clinic. This will greatly improve phenotyping in genetic research over the current methods using structured clinical assessments using standard categorical criteria; digital phenotyping is likely to be able to classify and refine human disease by analyzing physiological patterns (such as speech) over time. However, several confounding factors need to be addressed and the refinement of techniques developed in this study increases device comparability in determining the digital phenotypes.

Disclosure

Nothing to Disclose.

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T15. A NOVEL DATABASE UNDER CONSTRUCTION FEATURING SPATIOTEMPORAL EXPRESSION VARIATIONS AND CO-EXPRESSION ORGANIZATION IN HUMAN BRAIN

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Background: Gene expression of specific genes change over a lifespan, and also vary by tissue or cell types. Such variations are critical for normal structure and functions of the human brain. Deviation from a normal range likely contributes to etiology and pathology of neuropsychiatric disorders. But such normal range has never been defined. Additionally, gene coexpression may reflect regulatory organization relationships among genes. We also considered that gene co-expression might guide complex connection variations in different brain regions and development stages. Changes of co-expression have also been implicated in multiple psychiatric disorders. To capture the variations of individual genes and related co-expression modules in normal human brains, we are developing a novel database, named Brain Gene Expression Database (BrainExDB), serving the needs of common reference data of normal expression levels, variations, and co-expression organizations.
Methods: We collected 15 brain regions and six cell types of 1,258 brain samples from existing public databases and our data, including the Gene Expression Omnibus database, ArrayExpress, Genotype-Tissue Expression project, Brain Cloud, and Stanley. Stringent quality control was applied to remove low-quality data. Both microarray and RNA-seq data have been included. For studies containing samples of different ages and different brain regions or cell types, data were partitioned by their spatiotemporal groups. All gene expression data were normalized into ranking orders to represent their expression levels so that different studies were comparable. Each gene was recorded for its average rank order and variance of expression by brain regions, cell types, and age ranges whichever available. Finally, we analyzed the data by the weighted gene co-expression network analysis to get the co-expression modules. The hub genes and members of co-expression modules were also databased for query. By comparing data across different studies, we will also identify marker genes that significantly differ by cell types, brain regions, age, and sex.
Results: We will build a human brain expression database featuring gene expression levels and variance in brain cells and regions throughout a lifespan. The database will provide the marker gene list of cell type-, brain region-, age-, and sex-specific genes. The database will also provide gene co-expression module data. Data can be queried by the list of genes, with filters for specific brain regions, cell types, age range, and sex.
Discussion: We are compiling the biggest datasets of human brain gene expression, aiming to develop reference data that can be used in studying gene expression changes in neuropsychiatric brains. For the time-being, its immediate value is to offer the comprehensive information about expression levels and variance of specific candidate genes in specific brain regions, cell types, age range, and sex. The stability and validity for predicting case states will need to be evaluated by subset data of those patient brains in the same data collection, and from other sources. Furthermore, the marker gene lists and co-expression modules can be used for gene set analyses, and deconvolution analysis of mixed data.

Disclosure

Nothing to Disclose.

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T16. SOCIAL SUPPORT AND WELLBEING IN ADOLESCENCE ARE CORRELATED FOR GENETIC, AS WELL AS ENVIRO NMENTAL, REASONS

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Background: Adolescence is a critical period of biological, cognitive and emotional development. It is important that adolescents maintain good mental health and wellbeing at this stage to ensure a comfortable transition into flourishing adulthood, with better outcomes in a variety of domains such as work, relationships and physical health. At a phenotypic level, social support during adolescence is positively associated with wellbeing. Levels of support from peers and family also predict levels of depressive symptomology. This study aimed to investigate, for the first time, the extent to which genetic and environmental factors mediate the association between wellbeing and support in late adolescence. We present results from a wide range of wellbeing-related traits beyond the commonly investigated life satisfaction; this allows us to conduct a more nuanced exploration of the link between wellbeing and support.
Methods: A representative subsample of 1215 twin pairs from the Twins Early Development Study (TEDS) completed questionnaires relating to a variety of wellbeing and support measures at 18 years old. The bivariate twin method uses intraclass correlations from identical and fraternal twins to estimate phenotypic, genetic and environmental correlations between traits. We used structural equation model fitting to estimate model parameters through full information maximum likelihood and to assess goodness of fit of models and submodels.
Results: Heritability estimates ranged from 22% to 48% for wellbeing and support. Phenotypic correlations between wellbeing constructs and support were all in the expected positive direction. Genetic correlations were moderate to high (mean correlation = 0.54) while the environmental correlations tended to be much lower (mean correlation =

0.22). Shared genetic influences explained a larger proportion of the phenotypic correlations, ranging from 57% to 83%, than environmental factors. The positive and negative affect scales had lower genetic, environmental and phenotypic correlations with support compared to the other wellbeing measures. Life satisfaction and relatedness (a subscale of the Basic Psychological Needs scale) had higher phenotypic correlations with support and both were driven by higher shared environmental correlations.
Discussion: The strong shared genetic aetiology between wellbeing and support suggests that the two may share a biological pathway that leads to a common cognitive and/or emotional influence on both. For example, genetic influences on personality could affect both. Alternatively, one set of genetic influences could be having pleiotropic effects on the two constructs individually. The pattern of lower correlations of affect with support may be due to their more state-like nature. The higher phenotypic correlation between life satisfaction and support, and relatedness and support, can be explained by a greater overlap in environmental factors. Further research should explore what these environments are. Our findings have implications in the assessment of wellbeing interventions, many of which are designed to increase social interaction. The effectiveness of these interventions are most commonly assessed using life satisfaction. Greater attention should be paid to other wellbeing traits such as gratitude and meaning in life, as different effects may be seen. To ensure adolescents flourish, we will need to focus on improving all these aspects of wellbeing.

Disclosure

Nothing to Disclose.

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T17. THE GENETIC VARIANTS THAT INFLUENCE OUR HAPPINESS AND POSITIVE BEHAVIOURS ALSO INFLUENCE WHICH LIFE EVENTS HAPPEN TO US

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Background: Often, life events do not simply happen to us. As with other environments, we make them more or less likely through our behaviour, and that behaviour is partly influenced by our DNA. Previous research has shown that the genetic variants that influence negative behaviours also influence negative life events. We investigated whether the same is true for positive behaviours: do we seek out and construct the events of our lives partly because of genetic influences on our psychological wellbeing?
Methods: We collected a broad battery of positive psychological measures from over 9,000 16-year-old twins from the Twins Early Development Study (TEDS), including subjective happiness, life satisfaction, optimism, hopefulness, trust, competence, relatedness, autonomy, meaning in life, ambition, grit, curiosity, and gratitude, along with subjective health. The twins also responded to 20 items from the Coddington life events scale. We split these into positive and negative events using valence ratings given by the twins who had experienced the event and conducted bivariate twin analyses between life events and the 14 wellbeing traits.
Results: 22% of the population variance in positive life events can be explained by genetic variation, and 33% for negative life events. This can partially be explained by shared genetic influences between life events and psychological wellbeing. The wellbeing traits were positively genetically correlated with positive life events (mean r=0.21) and negatively genetically correlated with negative life events (mean r=-0.15). Those positive traits that drive behaviour (grit and ambition) showed highest genetic correlation with life events (r = 0.34 and 0.33 respectively), whereas the more reflective trait gratitude showed no significant correlation (r = -0.03).
Discussion: Our results suggest that genetic influences on active positive behaviours in particular may partly explain the heritability of life events, by prompting us to seek out or construct environments where they are likely to occur.

Disclosure

Nothing to Disclose.

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T18. A PRELIMINARY GENE BY ENVIRONMENTAL INTERACTION MODEL FOR CHILDHOOD-ONSET HIGH AGGRESSION

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Background: Both gene and environment have been implicated in the development of childhood aggression. The diathesis-stress hypothesis asserts that an individual's genetic predisposition interacts with stressful/ traumatic experiences to produce disordered behavior, including childhood aggression. Most gene-environment interaction studies have focused on the response of different genotypes of a single nucleotide polymorphism to various environmental stressors. The current study examines how these environmental stressors can interact with multiple genetic risk markers simultaneously to bring about childhood aggression problems.
Methods: Our sample consisted of 376 youths aged 5-17 (177 high-aggression cases and 199 non-aggression healthy

controls) of European ancestry as confirmed using 64 ancestry informative markers. The aggression cases had a history of disruptive behaviour for two years or more, scored at 90th percentile or more on the aggressive behaviour subscales of both the teacher and parent versions of the Child Behavior Checklist, and an intelligent quotient of at least 70 (WISC-III). A subsample of 126 children (60 cases, 66 controls) had valid information on traumatic experience using MAYSI-2. We analyzed 93 genetic markers identified based on previous literature and based on the number of genotyped cases and controls. The genetic markers associated with aggression was identified using chi-square tests. The genetic risk score was calculated by assigning a score of one for high-risk genotype group(s), and a score of zero for the low-risk genotype group(s) for each genetic marker and adding the scores across the associated genetic markers. We ran a logistic regression predicting case-control status using genetic risk scores and trauma exposure, controlling for sex and age.

Results: We found BDNF_rs61888800, Corticotropin-Releasing Hormone CRH_rs11996294, Corticotropin-Releasing Hormone Receptor CRHR2_rs3779250, Corticosteroid-Binding Globulin SERPINA6_rs3888305, and Oxytocin Receptor OXTR_rs237923 to be associated with child aggression individually ($p<0.1$). As expected, the genetic risk scores were significantly associated with high-aggression case-control status ($p<0.001$). Having genetic risks only (score of 2 or more on the genetic risk variable) with low trauma exposure (score of 2 or lower on the traumatic experience scale) did not increase the odds of developing problem aggression from those of children who had neither risk factor. The odds of developing aggression problems, however, were 6.3 times higher for children with trauma exposure only without the genetic risk ($p<0.001$), and 24.9 times higher for children with both the genetic risk and trauma exposure ($p<0.01$), compared to those of children with neither genetic risk nor trauma exposure.

Discussion: The study shows a significant gene-environment interaction in the development of childhood aggression when multiple genetic risks are examined simultaneously. Our next step is to examine whether these results can be replicated in a larger independent sample of children and in an adult aggression sample.

Disclosure

Nothing to Disclose.

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T19. POLYGENIC RISK SCORE ANALYSIS OF SUICIDAL BEHAVIOUR SEVERITY

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Background: Twin and family studies suggest that suicidal behaviour has a prominent genetic component. There have been a few genome-wide association studies (GWASs) of suicide attempt or suicidality with a few suggestive findings. Mullins et al (2014) reported a possible shared genetic component between suicidal ideation and major depression, but found suicide attempt to be at least partly distinct from mood disorder.

Methods: We carried forward our published GWAS of suicide behaviour severity scores, which ranged from suicidal ideation to serious suicide attempt, in bipolar disorder patients. We conducted polygenic risk score analyses of suicide behaviour severity scores in our discovery sample of 308 bipolar disorder patients using available GWAS results for major psychiatric disorders, including bipolar disorder, major depressive disorder, schizophrenia, attention-deficit hyperactivity disorder, and anxiety disorders, from the Psychiatric Genomics Consortium in PLINK.

Results: Preliminary findings from our polygenic risk score analysis suggest that genetic risks for attention-deficit hyperactivity disorder ($p<0.01$) and anxiety disorder ($p<0.05$) may be associated with suicide behaviour severity in our discovery sample of bipolar disorder patients.

Discussion: While suicidal behaviour and ADHD may have a possible genetic overlap, analyses of polygenic risk scores for specific symptoms of ADHD (hyperactivity/impulsivity versus inattention) may strengthen these findings. We will analyze for possible overlaps in genetic components between suicidal behaviour and other complex traits.

Disclosure

Patent application - JLK, CCZ

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T20. NEW INSIGHTS INTO THE PHARMACOGENOMICS OF ANTIDEPRESSANT RESPONSE FROM THE GENDEP AND STAR*D STUDIES: RESULTS OF RARE VARIANT ANALYSIS AND HIGH-DENSITY IMPUTATION

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Background: Genome-wide association studies have generally failed to identify polymorphisms associated with antidepressant response. Possible reasons are limited

coverage of genetic variants, phenotypic heterogeneity and small sample size.

This study investigated the genetic predictors of antidepressant efficacy in Genome-Based Therapeutic Drugs for Depression (GENDEP) and Sequenced Treatment Alternatives to Relieve Depression (STAR*D) samples trying to address some of the reported limitations. In detail: 1) coverage of genetic variants was increased by adding exome array data to previously available genome-wide data and by genotype imputation using the largest available reference panel (Haplotype Reference Consortium (HRC)); 2) a meta-analysis was performed using SNP methods and multi-marker tests at gene and pathway level.

Methods: Each dataset was imputed using Minimac3 and the HRC panel after standard quality control. Both samples included patients with diagnosis of major depressive disorder. In GENDEP, patients were partially randomized to escitalopram or nortriptyline; STAR*D patients were treated with citalopram. Escitalopram is the active isomer of citalopram, thus the whole GENDEP sample and the escitalopram-treated subgroup were meta-analyzed with STAR*D. The phenotypes were depressive symptom improvement and remission at week 12 according to standard scales. SNP-level analysis was performed using PLINK (pngu.mgh.harvard.edu/~purcell/plink/); gene and pathway analyses were performed using MAGMA (http://ctglab.nl/software/magma). Covariates were age, baseline severity, center of recruitment and ancestry-informative principal components. NEWMEDS (http://www.newmeds-europe.com) consortium samples, excluding GENDEP, served for replication.

Results: 7,062,950 SNPs were analysed in GENDEP (n=738) and STAR*D (n=1409). There was no evidence of genomic inflation (lambda values were $\leq$ 1.01). No SNP was associated with symptom improvement or remission in the full meta-analysis. In the citalopram/escitalopram analysis, rs116692768 (MAF=0.033, p=1.87e-08, ITGA9 or integrin alpha 9 gene) and rs76191705 (MAF=0.012, p=2.39e-08, NRXN3 or neurexin 3 gene) were associated with symptom improvement. At gene level (whole sample), OR4K2 was associated with improvement (corrected p=0.04), but its effect was inconsistent between the samples. At pathway level (whole sample), the Gene Ontology terms GO:0005694 (chromosome) and GO:0044427 (chromosomal part) were associated with improvement (corrected p=0.007 and 0.045, respectively). Genome-wide significant SNPs were not replicated in NEWMEDS SSRI-treated sample (n=751) (p>0.05).

Discussion: ITGA9 and NRXN3 show a meaningful biological rationale for being involved in antidepressant effect. ITGA9 codes for a membrane glycoprotein receptor for neurotrophins and NRXN3 is a transmembrane neuronal adhesion receptor involved in post-synaptic and pre-synaptic differentiation, with relevant implications for synaptic activity and synaptic plasticity. Interestingly, rs76191705 is a non-sense mediated decay transcript variant and a polymorphism in complete LD with it (rs79302561) acts as an enhancer of gene expression (Ensembl GRCh37 release 84). However, no convincing replication of these findings was achieved and further studies may be useful to clarify the role of these genes in antidepressant efficacy.

Disclosure

Nothing to Disclose.

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T21. HARM AVOIDANCE AND CHILDHOOD ADVERSITIES IN PATIENTS WITH OBSESSIVE-COMPULSIVE DISORDER AND UNAFFECTED FIRST-DEGREE RELATIVES: EVIDENCE FOR A DIATHESIS-STRESS MODEL

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Background: Obsessive-compulsive disorder (OCD) is a severe psychiatric disorder, which aggregates in families. Its etiology is assumed to involve interactions between genetically determined vulnerability factors and critical environmental influences. In the present study, we aim to investigate how the personality trait harm avoidance and the experience of different childhood adversities contribute to the development of OCD.

Methods: One hundred and sixty-nine patients with OCD, 157 healthy comparison subjects and 57 unaffected first-degree relatives of OCD patients were examined by trained clinical psychologists using the Structured Clinical Interview for DSM-IV (SKID). Harm avoidance was assessed using the Temperament and Character Inventory (TCI) and the severity of childhood adversities was measured with the Childhood Adversity Questionnaire (CTQ). Associations with depressive and obsessive-compulsive symptoms were investigated using the Beck Depression Inventory-II (BDI-II) and the Obsessive-Compulsive Inventory-Revised (OCI-R).

Results: Both OCD patients and unaffected relatives showed elevated levels of harm avoidance compared to healthy volunteers. Furthermore, patients exhibited significantly higher scores than relatives. This linear pattern was observed throughout all subscales of harm avoidance, and remained stable after controlling for the severity of depressive and obsessive-compulsive symptoms. With regards to childhood adversities, OCD patients reported higher levels than unaffected relatives and healthy volunteers, specifically on the subscales emotional abuse, emotional neglect, and experience of inconsistencies.

Discussion: The present findings support the role of harm avoidance as a potential endophenotype of OCD, and provide further evidence for a diathesis-stress model. While patients with OCD and unaffected first-degree relatives share elevated levels of harm avoidance, a heightened severity of childhood adversity was only observed in

patients. A predisposition to exaggerated anxiety responses may thus take different trajectories depending on adverse environmental influences during childhood. In future research, we aim to investigate the genetic and epigenetic mechanisms underlying these findings.

Disclosure

Nothing to Disclose.

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T22. NEXT-GENERATION BISULFITE SEQUENCING OF CACNA1C WITH ILLUMINA MISEQ

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Background: The complex etiology of psychiatric illness involves both genetic and environmental factors. The latter may act via epigenetic processes such as DNA methylation. Studies suggest that epigenetic regulation of gene expression may mediate the effects of early life experiences on adult behavior and susceptibility to psychiatric illness. CACNA1C is an epigenetically regulated gene implicated in the etiology of psychiatric illness. Here, the third CpG island located in intron 3 is of particular interest since: (1) differential methylation is reported between bipolar patients and controls, with higher methylation levels being observed in patients; (2) CpG sites in this CpG island show blood/brain correlation; (3) individual methylation level predict more of the variance than tissue methylation level; and (4) it is a significant meQTL, as it is located in close proximity (5kb) to rs1006737, which shows a genome wide significant association to bipolar disorder, schizophrenia, and major depression. The aim of the present study was to test the feasibility of next generation bisulfite sequencing in the methylation analysis of CpG sites of the third CACNA1C CpG island.

Methods: Next generation sequencing (NGS) analysis of the CACNA1C region of Intron 3 was performed. A total of 63 CpG sites from three bisulfite converted whole blood DNA samples were analyzed. Both single- and multiplex-PCRs were used.

Results: Singleplex-PCR generated 8,000 to 36,000 sequence reads, with a sequence identity of 99.0 to 99.9%. The standard deviation of the methylation level per CpG of the three samples ranged from 0.3 to 6.4%. Multiplex-PCR generated variable methylation values, with lower sequence identity and fewer sequence reads.

Discussion: This is the first comprehensive analysis of methylation levels of the CACNA1C third intronic region to use NGS. The results indicate that multiplex PCR is not an appropriate method for methylation analysis of bisulfite converted DNA. Now it is planed to perform simultaneous sequencing of 384 samples using singleplex-PCR.

Disclosure

Nothing to Disclose.

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T23. POLYGENIC RISK SCORES DERIVED FROM LARGEST SCHIZOPHRENIA GWAS ARE ASSOCIATED WITH THE PRESENCE OF PSYCHOSIS AND LEVEL OF MOOD INCONGRUENT PSYCHOSIS IN BIPOLAR DISORDER

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Background: Bipolar disorder (BD) includes a broad range of phenotypic features – most research examining its genetic underpinning focuses on the overall syndrome rather than its subphenotypic components. BD is a highly heritable disorder and while its genetic architecture is not fully elucidated there is increasingly strong support for a very polygenic component with partial polygenic overlap with schizophrenia (SZ). Here we present preliminary results from an analysis examining the association of SZ derived polygenic risk scores (PRS) across different BD subtypes (Bipolar Type 1(BPI), Bipolar Type 2 (BPII) and Schizoaffective disorder (SAD), and subphenotypes defined by the presence of psychosis and its associated level of mood incongruence.

Methods: We used a UK sample of 3101 BP cases, collected using a consistently administrated interview protocol with

OPCRIT confirmed lifetime diagnosis of Research Diagnostic Criteria (RDC - BPI, BPII or SAD). PRS were generated using 1000 genomes (phase3, 2014) imputed genetic data (INFO score > 0.8, HWE > 1e-6, MAF > 0.01) trained on the results from Psychiatric Genetic Consortium (PGC2) SZ GWAS, pruned r2 < 0.25, and computed across different SZ association p-value thresholds (range 0.0001 - 0.5). PRS were standardised and analysed with nominal logistic regression with RDC subtypes as dependant variables. To test whether psychosis mediated the association across subtypes, we repeated the analyses fitting psychosis together with PRS in the model and comparing it with the PRS only model. We also examined SZ-PRS association with psychosis in the whole sample and level of mood incongruent psychotic features in the subset of cases with psychosis (n = 1352). All regression models were adjusted for age, sex and 1st 10 principal components derived from genetic data. Above analyses was run using DSM and ICD

Results: PRS with the SZ association p-value cut-off of 0.5, have shown significant association across the BD subtypes with relative risk ratios RRR = 1.28 (95%CI: 1.18-1.39, p < 0.0001) and RRR = 1.18 (95%CI: 1.01-1.38, p = 0.03) for BP1 and SAD, respectively, compared to BP2 as the baseline. Entering psychosis into the model attenuated the effect of PRS in the BP1 group but still remained significant (RRR = 1.19, 95%CI: 1.08-1.31, p < 0.0001). In contrast the effect in the SAD group has become insignificant (RRR = 1.05, 95%CI: 0.89-1.24, p = 0.6). In the whole sample of BD cases, PRS has shown association with presence of psychosis RRR = 1.23 (95%CI: 1.15-1.34, p < 0.0001). Examining cases with psychosis, we found PRS was associated with increasing level of mood incongruence (OR = 1.15, 95%CI: 1.04-1.27, p = 0.005). The results are ostensibly the same when PRS are generated using p-value thresholds from the range 0.05 - 0.5 , indicating these results are mostly driven by SNPs identified at p < 0.05. Analyses using DSM and ICD show similar results.

Discussion: Preliminary analyses show a genetic - phenotypic association, between polygenic features of schizophrenia and BP characterised by the presence of psychosis, suggesting the phenotypic overlap between SZ and BD may in part be driven by polygenic overlap. This finding is further supported by the association of PRS and level of mood incongruence in the content of psychotic symptoms. These results suggest the PRS effect is not solely mediated though the psychosis subphenotype, at least in the BPI group. Our analyses show promise for the strategy of examining polygenic/phenotypic associations based on fine grained clinical characterisations

Disclosure

Nothing to Disclose.

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T24. SEX-SPECIFIC DNA METHYLATION SIGNATURES IN PANIC DISORDER

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Background: Panic disorder (PD) is characterized by sudden episodes of acute anxiety occurring without any apparent reason. PD is the most disabling anxiety disorder and it affects twice as many women as men. The heritability of PD is estimated to be up to 48% and epidemiological studies show that both cumulative and specific life events are risk factors for the development of PD. Therefore, the investigation of genetic factors and gene-environment interaction is of high importance for understanding the pathophysiology of PD. As such, examining epigenetic differences in PD patients is of great interest given that environmental factors, in combination with genetic variation, can influence DNA methylation.

Methods: We conducted an Epigenome-Wide Association Study (EWAS) comparing non-medicated PD patients (49 females, 40 males) with healthy controls (48 females, 28 males). Replication was sought in an independent sample (131 cases, 190 controls) and further confirmed with a meta-analysis across both samples (220 cases, 266 controls). DNA methylation levels were assessed in whole blood using the Infinium HumanMethylation450 BeadChip. Failed probes were excluded based on a detection p-value larger than 0.01 in > 50% of the samples. X chromosome, Y chromosome and non-specific binding probes were removed. The data were normalized with functional normalization in Minfi and batch-corrected using ComBat. Regression analyses accounting for cellular heterogeneity, sex and age were performed to test for associations between PD status and DNA methylation. To further assess functionality of the significant CpG, gene expression profiles (Illumina HumanHT-12 v3.0 array) in peripheral blood before and after exposure to the glucocorticoid receptor agonist dexamethasone were tested for association with DNA methylation in another independent female sample (N = 71).

Results: No genome-wide associations were observed in PD patients compared to controls in the whole sample. Interestingly when stratified by sex, only the comparison of female PD patients with controls yielded one genome-wide association surviving FDR of 5% (P = 1.094 x 10-7 , P-adj = 0.046). Specifically, cg07308824, located in the promoter of the HECA gene, was hypermethylated in female PD patients (N = 49) compared

to controls (N=48). The same CpG was also hypermethylated in female PD patients in the replication sample (P=0.035) and the genome-wide significant association was confirmed in the meta-analysis (P-adj=0.007). Methylation at this CpG site was associated with mRNA expression of HECA both at baseline (P= 0.046) and after induction by dexamethasone (P= 0.029). Pathway analyses using Web Gestalt investigating the top 50 associated CpG sites showed enrichment in female-specific pathways, e.g. female infertility pathways.

Discussion: Our study is the first to examine epigenome wide differences in peripheral blood for PD patients. Interestingly, our results point to possible sex-specific and functional methylation changes in PD. Further studies are needed to examine a possible contribution of the HECA gene methylation to female specific factors in PD.

Disclosure

Nothing to Disclose.

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T25. THE VAL66MET BDNF GENETIC POLYMORPHISM DOES NOT MODIFY THE ASSOCIATION BETWEEN MAJOR DEPRESSION AND BODY MASS INDEX (BMI)

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Background: Depression and obesity are highly prevalent diseases in the general population, responsible of disability burden worldwide. Recently, a bidirectional relationship between both disorders has been described but the biological explanation of this reciprocal link is still unknown. The association between the BDNF Val66Met polymorphism and depression has been described in several studies. Besides, this polymorphism has also been associated with eating behavior, eating disorders and body mass index (BMI). The aim of this study is to investigate the genetic influence of the BDNF Val66Met polymorphism in relation to BMI in a population-based sample of individuals with major depression versus controls.

Methods: We performed a case-control study including 337 individuals with major depression and 921 healthy controls from the Granad∑p and PISMA-ep studies from the region of Andalusia (Spain). The MINI was used to establish the diagnostic of depression. Height and weight data reported from each individual was used to calculate BMI using the formula: weight(kg)/height(m)2. T-tests were used to analyze the association between major depression and BMI. Linear regression models for quantitative traits assuming an additive genetic model were applied to analyze the association between the BDNF Val66Met polymorphism and BMI. First, the analyses were carried out in the whole sample, and then separately in cases and controls. The regression analyses were adjusted by sex, age, province and depression status in the whole sample. When cases and controls were analyzed separately, sex, age and province were included as covariates in the models. Finally, we performed interaction analysis between the Val66Met polymorphism, major depression and BMI. The statistical analyses were carried out with the software PLINK v1.06.

Results: We found a statistically significant association between major depression and BMI. The individuals with depression had significantly higher BMI values compared to controls (cases: BMI=27.54 (SD=5.75); controls: BMI=26.75 (SD=4.76); t=-2.34, P=0.009). No significant differences were found in the allelic or genotypic frequencies distribution when cases and controls were compared.

Linear regression analyses did not show a significant association between the Val66Met polymorphism and BMI, neither in the whole sample (β=-0.1035, p=0.651) nor when cases and controls were analyzed separately (cases: β=-0.791, p=0.134; controls: β=-0.177, p=0.470). No interaction between the Val66Met polymorphism and major depression was found in relation to BMI (β=-0.787, P=0.14).

Discussion: Our results show an association between BMI and major depression confirming the results from previous studies. However, our study does not support the implication of the BDNF Val66Met polymorphism in the genetic relationship between BMI and major depression.

Disclosure

Nothing to Disclose.

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T26. BRIEF ASSESSMENT OF MAJOR DEPRESSION FOR GENETIC STUDIES: VALIDATION OF CIDI-SF SCREENING WITH SCID INTERVIEWS

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Background: Studies of common genetic variants in complex psychiatric disorders such as major depression require samples that are too large (tens or hundreds of thousands) than can typically be collected with phenotyping methods involving direct interviews by trained clinicians. Many studies are no identifying cases and controls with self-report questionnaires, electronic medical records or registry data. Few data are available to determine the accuracy of these methods compared to direct interviews. Here, we present data on 1,263 individuals for whom online "screening" and direct interview data were available.
Methods: The Depression Genes and Networks study (DGN) recruited cases with recurrent MDD and controls with no lifetime MDD for a study of whole-blood gene expression. A research company emailed invitations to 14,463 survey panel members; 9,569 completed an online screen including the CIDI-Short Form depression and substance dependence modules, of whom 1,263 eventually gave blood samples and completed telephone SCID-IV interviews: 669 prospective cases (CIDI-SF recurrent MDD without current substance dependence) and 594 prospective controls (no 2-week period of depression or anhedonia with >2 MDD criteria; no current substance dependence). For this analysis we also identified narrow screening criteria for controls (no 2-week period with both depression and anhedonia; or one of these but not most of the day, nearly every day; no lifetime antidepressant [AD] use [SCID]). Polygenic score predictions were then examined in the GenRED-I GWAS cohort (which used non-overlapping controls screened with CIDI-SF) using broad vs. narrow controls.
Results: Among prospective cases, SCID diagnosis was MDD recurrent (N=547, 81.2%; some were excluded from DGN for other reasons) or uncomplicated single episode (39, 5.8%) totaling 87% with diagnoses that would be included in most genetic studies of MDD; 18 (2.7%) had major depressive episodes with complications that would typically be excluded (bereavement, medical or substance-related factors), and 65 (9.7%) had such exclusions as bipolar disorders (28, 4.2%), no MDD (30, 4.5%), or unreliable histories (7, 1%). Among prospective controls, 108 (18.2%) were excluded by SCID, primarily for MDD (57, 9.6%), sub-threshold depression (25, 4.2%), or a bipolar disorder (6, 1%). Narrow screening criteria would have excluded 76 (70%) of the 108 ineligible controls (57 by CIDI-SF clinical screening, 19 for self-reported AD use) and 44 (9.1%) of the SCID-eligible controls, thus predicting 93.2% validation by SCID. PRS prediction was improved in the GenRED cohort using only narrow controls.
Discussion: Online CIDI-SF screening for MDD-R has a high rate of validation by SCID interviews: 81.8% for MDD-R, and 87.6% if uncomplicated single-episode MDD is considered part of the genetic spectrum. Only 4.5% had no major depressive episode by SCID, but 4.2% received bipolar diagnoses. Although self-report screening for mania is only modestly accurate, we recommend using it to increase the proportion of true positive cases. The false-positive rate in controls could be largely controlled by using a very strict threshold for self-reported history of depression (basically, not endorsing depression screening items) and by excluding for any self-reported antidepressant use. This excludes a small proportion of "true" controls, but an excess of prospective controls is typically available

Disclosure

Nothing to Disclose.

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T27. FROM PERSONALITY TRAITS AND INTERLEUKIN LEVELS TO GENETIC MARKERS OF MOOD DISORDERS SPECTRUM IN ADOLESCENTS AND YOUNG ADULTS

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Background: Data in literature support the inflammation component in Bipolar disorder (BD). Stress may induce inflammatory changes in the immune system by activating the hypothalamic-pituitary-adrenal (HPA) axis. Recent studies confirmed that genetically determined personality traits are responsible for personal resources of stress resistance and thus they can play an important role in bipolar disorder development especially in young patients. There is no doubt that BD is a complex mental illness with a relevant genetic component. However, previously used strategies to identify genetic biomarkers have not produced the expected results. Actually there is no biological markers that can help to early diagnose and effective pharmacotherapy especially in adolescents and young adults. GWAS skip genes with relatively little impact on the disease. They prevent therefore identify genes in psychiatric disorders with cumulative polygenic inheritance and epigenetics influences. That's why we made an attempt to reverse the methods by “from candidate gene to protein” to “from protein to candidate gene” with regard to personality traits.

Methods: 33 patients (aged 12-24), with a diagnosis MD meeting spectrum BD criteria, were included to this study. Participants were assessed by using structured diagnostic interviews according to ICD-10 and DSM-IV and completed the Temperament and Character Inventory (TCI). The evaluation was conducted in the state of severity of the symptoms (visit 0) and after reaching the stabilize mood (visit K). We studied a panel of 6 cytokines (IL-1β, 2, 4, 6, 8 and 10), known to interact with BD. Serum concentrations of all these molecules were measured using the commercial available DIAplex kit. The genes selection for analyzes includes multi-level approach with use of the own results of personality traits measure and cytokines level obtained in patients with BD spectrum from Polish population as well as databases and pathway analysis using in silico tools.
Results: Comparing the results of patients at 0 to K no significant differences in cytokine serum levels were observed. Correlation analysis showed a significant higher IL-8 serum levels in non-depressed vs depressed patients ($p=0.017$) as well as higher concentration of IL-6 in young adults (18>years) compared to teenagers ($p=0.030$). Patients at 0 obtained higher score in Harm Avoidance (HA) dimension ($P=.023$). Correlation analysis of cytokine serum concentration and main dimension of personality traits showed significant positive relationship between IL-2 and persistence (P) ($p=0.017$) as well as negative relationship between IL-6 and Self Transcendence (ST) ($p=0.035$).
Discussion: Obtained results indicates that interesting candidate genes to association study may be IL-2,6 and 8. However most promising connector of all analyzed traits in analyzed group is IL-6. In silico analyses according to i.e. gene prospector and other free available data bases confirms that IL-6 is strong candidate gene for association analysis including gene expression in the lymphocytes of patients with bipolar disorder. IL-6 is able to activate HPA axis and is involved in the development of despair-like behaviors triggered by inflammation. The single nucleotide polymorphism (SNP) rs1800795 (-174 G/C) and rs1800796 (572G>C) known from inflammatory autoimmune disease were not analyzed in bipolar disorder.

Preliminary results suggest that proposed approach should be used in reanalysis on a larger study group to enable genotyping and association analysis.

Disclosure

Nothing to Disclose.

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T28. EPIGENOME-WIDE ANALYSIS OF METHYLATION AND PERCEIVED PARENTING IN ADOLESCENTS AND ITS CORRELATION WITH DEPRESSIVE SYMPTOMS OVER TIME

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Background: Adolescents are continuously exposed to their parents. Previous research has shown that parenting can affect adolescents' wellbeing. Prior research has also argued that adolescents' impaired wellbeing can influence their performance over time. We present a study with an Illumina 450k array comparing methylation in adolescents reporting either perceived supportive-guiding or punishing-neglecting parenting at T0 and how these methylation differences are correlated with depressive symptoms over time.
Methods: Following a cluster analysis with a 6 cluster solution, 45 Belgian adolescents (Mage (SD) = 13.88 (0.90) at T0; 48% boys) from the STRATEGIES dataset (n= 1116) were randomly selected from the two most extreme clusters: perceived supportive-guiding parenting qnd punishing-neglecting. Perceived parenting was measured with the Leuven Adolescent Perceived Parenting Schale (LAPPS) and the Parental Behavior Scale (PBS). Methylation was measured with an Illumina Infinium HumanMethylation450 BeadChip. 1 individual was excluded after quality control (RnBeads, R), resulting in 44 adolescents for analysis. DMRs were identified using DMRcate (R) and comb-p (Python). We corrected for gender, batch, cell types (Horvath), and hidden stratification. The accuracy of the 450k-array was verified with Sequenom Epityper (min. r=.46, max. r= .97; $p < .0062$). Depressive symptoms were assessed on a yearly basis using the CES-D scale (Centre for Epidemiologic Studies Depression Scale). Correlations between the most significant CpG per region (17 CpGs, tested based on clusters T0) and the depression score two years later (T2) were calculated with Pearsons' correlations.
Results: Only DMRs overlapping between the top 20 of DMRcate, ranked by "minpval" and comb-p at the e-2 (14 DMRs) and e-3 level (28 DMRs), were taken into account. Despite the major statistical differences in the two approaches, 13 DMRs overlapped between DMRcate and comb-p at the e-3 level. 4 additional DMRs overlapped

when adding the e-2 level. Regions are annotated to the genes PEX10, ASCL2, KCNQ1, GPR19, DLL3, HDAC4, RFPL2, PPT2, ACAT2, KIF25, HOXA11, PTPRN2, and SCRIB. For the most significant CpG per region, only three CpGs were correlated with depressive symptoms at T2: cg13306335 in PEX10 ($r = .47$, $p = .0014$), cg05171197 in HDAC4 ($r = .33$, $p = .021$) and cg13417420 in GPR19 ($r = .33$, $p = .030$), with PEX10 surviving Bonferroni correction for 17 tests ($p < .0029$). The two parenting clusters of interest at T0 were correlated with depressive symptoms at T2 by $r = 0.33$ ($p = .025$).

Discussion: Despite our limited sample size, we show that two statistically different methods overlap highly in the regions they identify to be significantly different based on perceived parenting in this adolescent sample. Furthermore, we show that for PEX10 the methylation at the most significant CpG is more strongly correlated with depressive symptoms two years later (T2) than the cluster at T0 and depressive symptoms at T2. This raises the question if parenting in adolescents can affect methylation at T0, which may secondarily predispose some adolescents to depressive symptoms over time. More research in a larger and independent sample is needed to validate this preliminary hypothesis.

Disclosure

Nothing to Disclose.

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T29. GSK-3B 50 T/C POLYMORPHISM AND LITHIUM MAINTENANCE TREATMENT IN BIPOLAR DISORDER

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Background: Bipolar Disorder is a chronic debilitating mental illness requiring long term medications. Bipolar disorder also has heritability of 80%, thus probably indicating an underlying genetic etiology.

Glycogen Synthase Kinase (GSK) is a serine/threonine kinase. GSK3-b is an essential element of the Wnt/beta-catenin pathway.

GSK-3B gene has been mapped to chromosome 3q13.3, a potential susceptibility locus for bipolar disorder. GSK-3B 50 T/C single nucleotide polymorphism (SNP) falls into the effective promoter region (nt − 171 to + 29) of the GSK-3B gene and the presence of T allele is noted to increase the transcriptional activity.

GSK-3B is also directly inhibited by Lithium which is widely used in the prophylaxis of Bipolar Disorder. Earlier Studies have also found a positive correlation between Mutant C allele carriers of 50 T/C SNP and better response to Lithium.

Methods: 441 patients with Diagnosis of Bipolar Disorder according to DSM-IV were recruited from all patients attending Outpatient Services of National Institute of Mental Health and Neurological Sciences (NIMHANS). The diagnosis was confirmed using Clinical Interview and MINI 5.0.0. Genotype analysis for 189 patients selected was done for GSK-3B -50 T/C using PCR-RFLP method. Treatment response has been assessed using "Retrospective Criteria of Long Term Treatment Response in Research Subjects with Bipolar Disorder" for 95 patients for whom NIMH life charts were available

Results: Of all the 441 patients who were selected for the study, demographic analysis was done with the mean age at onset being 21.40 years (SD- 6.940). Lifetime psychotic symptoms were noted among 377 subjects.

The genotype Frequencies for the GSK-3B 50 T/C polymorphism CC-25.9%, TC-47.6%, TT-26.5% for 189 patients, did not deviate significantly from Hardy-Weinberg equilibrium. Of the patients who were C allele carriers ($N=78$) there were 14 subjects who were poor responders (score less than or equal 3) and 64 subjects who were good responders (score >3).However this difference was not significant($p>0.05$,Spearman's correlation $p>0.05$).

No statistically significant correlation was found between GSK-3B 50 T/C SNP and the clinical parameters that were studied including age at onset($n=186$), and presence of psychotic symptoms($n=186$) (all $p>0.05$)

Discussion: The study did not duplicate the favorable response to Lithium among patients who carry C allele in GSK-3B 50T/C SNP using a well validated scale to assess lithium response like "Retrospective Criteria of Long Term Treatment Response in Research Subjects with Bipolar Disorder" scale probably owing to difference in the allelic frequencies in the studied population. In a previous study by Benedetti et al,2008 among 60 Caucasian subjects had CC- 5%, TC-40%, TT-55% which significantly varies with the frequencies noted in the studied population. The limitation being that study was under-powered to assess the allelic association and a larger study is being completed currently.

The study though did not find any positive association of GSK-3B 50 T/C with other clinical parameters that were studied. No other previous studies have looked into the association between the studied SNP and clinical parameters of Bipolar Disorder in this population.

We are also in the process of doing gene expression analysis from cell lines (lymphoblastoid, induced pluripotent) derived from patients with this SNP to obtain further insights into the mechanism of Lithium in bipolar disorder.

Disclosure

Nothing to Disclose.

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T30. THE ROLE OF CIRCULATING MICRORNAS AS POSSIBLE BIOMARKERS PREDICTING RESPONSE AND ADVERSE EVENTS IN DEPRESSED AND ANXIOUS CHILDREN AND ADOLESCENTS TREATED WITH FLUOXETINE

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Background: Depression and anxiety disorders are among the most common childhood psychiatric disorders. Selective serotonin reuptake inhibitors (SSRIs) are generally considered first-line treatment for both depression and anxiety in this age group. However, it has been reported that 30%–40% of all patients who receive a sufficient dose and duration of treatment fail to respond. Moreover, SSRI use is frequently associated with serious adverse events (AE), including activation symptoms, manic switch and increased suicidal behavior. These are particularly relevant in pediatric populations because of concerns about the suicide threat of SSRIs, resulting in a black-box warning. Currently there is no way of knowing in advance who of the patients will respond or develop AE. The purpose of the current study is to examine the role of circulating small non-coding RNA's (ncRNA's) as a promising candidate biomarker for SSRI treatment response and AE in children and adolescents treated for depression and anxiety disorders.
Methods: Eighty patients who met DSM-IV criteria for major depressive disorder (MDD) or anxiety disorders participated in the study. Their age ranged from 6 to 18 (14.12 $\pm$ 2.30) years. The patients were treated with fluoxetine 20-40 mg/day for 8 weeks. Psychiatric evaluation was conducted using several standardized diagnostic instruments. The changes in depressive and anxiety symptoms from baseline to 8 weeks were assessed, and remitters and non-responders were compared. Suicidal events, as per convention in pharmacological trials, were defined as either a suicide attempt or an onset or worsening in suicidal ideation. Activation was assessed using a new scale devised by our group for the project and mania by the Young Mania Rating Scale. Blood samples from all the participants were collected before treatment initiation and after eight weeks. RNA was purified using QIAGEN kit and libraries were prepared for sequencing using the Illumina TruSeq Small RNA Library Preparation Kit. miRBase based quantification of miRNAs was carried out on each sample. Samples with less than 1,000,000 miRNA reads were excluded. DeSeq2 was performed for statistical analysis.
Results: The overall response rate was 67%. Seventeen children and adolescents (21%) responded with moderate or severe AE. In total 86 samples were analyzed. Ten differentially expressed miRNA's were found between the responders with no AE vs. non-responders/responders + moderate or severe AE.
Discussion: Ongoing studies: A recruitment of a new cohort of children for validation of the finding in the first cohort will follow. The differentially regulated small ncRNA's will form the basis of a study in an animal model of juvenile depression which will hopefully enable us to gain insights into the mechanism of how these models are involved in the biology of response to treatment and perhaps even of juvenile depression.

Disclosure

Nothing to Disclose.

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T31. GENES INVOLVED IN NEURODEVELOPMENT, NEUROPLASTICITY AND BIPOLAR DISORDER: CACNA1C, CHRNA1 AND MAPK1

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Background: Bipolar Disorder (BPD) is a common and severe mental disorder. The involvement of genetic factors in the pathophysiology of BPD is well known. In the present study we tested the association of several SNPs within three strong candidate genes, CACNA1C, CHRNA7 and MAPK1, with BPD. These genes are involved in monoamines-related pathways as well as in dendrites development, neuronal survival, synaptic plasticity and memory/learning.
Methods: One hundred and thirty-two (132) subjects diagnosed with BPD and 326 healthy controls of Korean ancestry were genotyped for 40 SNPs within CACNA1C, CHRNA17 and MAPK1. Distribution of alleles and block of haplotypes within each gene were compared in cases and controls. Interactions between variants in different loci were also tested.
Results: Significant differences in the distribution of alleles between the cases and controls where detected for rs1016388 within CACNA1C, rs1514250, rs2337980, rs6494223, rs3826029 and rs4779565 within CHRNA7 and rs8136867 within MAPK1. Haplotype analyses also confirmed an involvement of variations within these genes in BPD. Finally, exploratory epistatic analyses demonstrated potential interactive effects, especially regarding variations in CACNA1C and CHRNA7.
Discussion: Overall, our data suggest a possible role of these three genes in BPD. Alterations of one or more common brain pathways (e.g. neurodevelopment and

neuroplasticity, calcium signaling) may explain the obtained results. However, a limited sample size and the consequential risk of false positive findings should be taken into consideration when evaluating this data.

Disclosure

Nothing to Disclose.

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T32. INVESTIGATION OF FAMILIAL CO-AGGREGATION AND GENETIC CORRELATION OF AGE AT ONSET AND EPISODICITY WITH PERSONALITY DIMENSIONS IN MAJOR DEPRESSIVE DISORDER

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Background: Personality dimensions have been shown to be heritable and are linked to liability of psychiatric disorders. Neuroticism, in particular, has a pervasive association with major depressive disorder (MDD) partially explained by shared genetic effects. Neuroticism predicts the clinical presentation and comorbidity of MDD, the onset of new episodes and affects its course and response to treatment. Age at onset (AAO) and episodicity, widely considered as proxies of disease severity, are both familial and heritable (Ferentinos et al. 2015) hence providing clues to dissecting MDD heterogeneity. A recent meta-analysis of GWAS of neuroticism by the Genetics of Personality Consortium (GPC; de Moor et al. 2015) pinpointed a genome-wide significant SNP in MAGI1 previously associated with episodicity in MDD (Ferentinos et al. 2014). The aims of this study were: first, to investigate the familiality of personality dimensions and their co-aggregation with AAO and episodicity within families of MDD siblings; second, to assess the SNP-heritability of personality dimensions and their genetic correlations with AAO and episodicity in unrelated genotyped MDD subjects.
Methods: Personality dimensions (neuroticism-N, extraversion-E, psychoticism-P) were extracted from the Eysenck Personality Questionnaire (EPQ). For our first aim, we used 1498 subjects with recurrent MDD from the DeNt affected siblings study (691 families with 2-5 affected full siblings). Familiality of EPQ dimensions was investigated with linear mixed models (LMMs). We then created a dataset of all possible sibpairs and calculated cross-trait within-subject and cross-trait cross-siblings associations of AAO and episodicity with each EPQ dimension. Analyses were performed with LMMs or negative binomial generalized linear mixed models (GLMMs) for AAO or episode frequency, respectively and applying a family size weight to adjust for non-independence of sibpairs (Suarez & Van Eerdewegh, 1984). For our second aim, we used 2695 unrelated MDD cases from the RADIANT studies. AAO, episodicity and EPQ scores were similarly analyzed in LMMs or GLMMs as appropriate. Derived residuals were then used to estimate SNP-heritabilities of EPQ scores or their pairwise genetic correlations with AAO and episodicity in GREML bivariate analyses with GCTA software.
Results: In the DeNt dataset, all personality dimensions were familial, with intraclass correlation coefficients (ICCs) of 0.21 (SE 0.04), 0.11 (SE 0.03) and 0.17 (SE 0.04) for N, E and P scores, respectively. AAO was negatively associated with neuroticism ($p<0.001$) and psychoticism ($p=0.004$) while episodicity was positively associated with neuroticism ($p<0.001$) within subjects. However, cross-siblings associations were significant only between episodicity and neuroticism ($p=0.031$). GREML analyses in unrelated cases were underpowered for estimating SNP-heritabilities of personality dimensions (power=0.16 for estimating a heritability of 0.15) and their genetic correlations with AAO and episodicity.
Discussion: Neuroticism and episodicity co-aggregate within families of siblings with MDD. Larger samples are required to test whether this familial covariation is due to shared additive genetic effects. As a next step, the predictive accuracy of GPC personality polygenic scores on AAO and episodicity in the RADIANT study is being tested.

Disclosure

Nothing to Disclose.

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T33. SERUM PHOSPHATIDYLINOSITOL AS A BIOMARKER FOR BIPOLAR DISORDER LIABILITY

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Background: There is increasing evidence that individuals with bipolar disorder (BPD) have abnormal serum

phospholipid levels. However, it is unclear whether these alterations arise as a secondary consequence of illness state, or if phospholipids share genetic etiology with illness risk. If the latter supposition were true, then phospholipids and their underlying biochemical mechanisms might provide key insights into the pathophysiology of the illness. Therefore we rank-ordered phospholipid classes by their genetic overlap with BPD risk in order to establish which class might be most informative in terms of increasing our understanding of illness pathophysiology.

Methods: Analyses were conducted in a sample of 1131 individuals, unselected for BPD, from extended pedigrees (average family size = 27.67, range = 2-128). We calculated a coefficient of relatedness for all family members of 9 individuals with BPD in the sample (N = 283). Then under an endophenotype ranking value (ERV) approach this scalar index was tested against thirteen serum-based phospholipid concentrations in order to rank order lipid classes by their respective overlap with BPD risk.

Results: The phosphatidylinositol class was significantly heritable (h2 = 0.3111, p = 5.19x10-12). It was the top-ranked class, and was significantly associated with BPD risk after correction for multiple testing (β = -1.032, p = 3.28x10-03, ERV = 0.4203).

Discussion: We identified a peripheral biomarker, serum-based phosphatidylinositol, which exhibits a significant association with BPD risk. Therefore, given that phosphatidylinositol and BPD risk share partially common etiology, it seems that this lipid class warrants further investigation, not only in terms of treatment, but also as a promising diagnostic and risk marker. This is the first study to investigate shared genetic overlap between phospholipid levels and bipolar disorder risk.

Disclosure

Nothing to Disclose.

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T34. NEUROPEPTIDE RECEPTOR GENE (NPSR1) POLYMORPHISM AND SLEEP DISORDERS

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Background: To study the association polymorphism gene of candidate NPSR1 rs324981 with sleep disorders in the open population of men 45-64 years of Novosibirsk.

Methods: The study of the association candidate gene polymorphisms with sleep disorders was carried out during the examination of a random representative sample of men 45-69 years (n = 1770). The response rate was 61%. The median age is 56.5 year. Every 12 subject was selected for genotyping (n = 147). To assess the level of sleep was used a questionnaire which was filled with self-test. Statistical analysis was performed using SPSS-11.5.

Results: The level of sleep disorders in the male population of 45-64 years was 79.9%. The frequency of homozygous C / C genotype of neuropeptide S (gene NPSR1 rs324981) was 19.4%, T / T genotype occurs in 27.8%, C / T genotype - 52.8%.

Men dominated the T allele of -54.2%, and the C allele - 45.8% growth trend Fnd dissatisfaction with the quality of their sleep among men. Men T- allele carriers, most evaluated their sleep as "satisfactory" in 69% of cases, (χ2 = 15,713 df = 8, p $<$0.05).

Discussion: Association found men carrier T - allele of neuropeptide S (gene NPSR1 rs324981), a sleep disorder.

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T35. MICRORNA REGULATION OF CANDIDATE GENES FOR TOURETTE SYNDROME

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Background: Tourette Syndrome (TS) is a neurodevelopmental disorder that presents early in childhood and is marked by the appearance of multiple involuntary motor tics and at least one vocal tic. It presents high comorbidity rates with other disorders such as attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD). Despite a strong genetic contribution, the molecular mechanisms behind TS are still uncertain, although multiple lines of evidence suggest involvement of specific candidate genes and corresponding epigenetic mechanisms via miRNA regulators.

Methods: To date only a few genetic findings have been replicated in TS. Among these the nicotinic acetylcholine receptor alpha 7 subunit (CHRNA7) gene has been recently suggested as candidate susceptibility gene. CHRNA7 is known to regulate a wide variety of developmental and secretory functions, however, the mechanism of its transcriptional regulation is still unclear [1]. Another recent promising finding in TS genetic research is Netrin 4 (NTN4),

which belongs to a family of extracellular proteins that direct axon outgrowth and guidance [2]. Several microRNAs have already been associated with neuropsychiatric disorders, but most importantly a few miRNA have also been associated with Tourette Syndrome [3,4].Our goal was to investigate the role of selected candidate genes in a case-control setup along with functional validation involving miRNA regulation in the possible involvement in TS pathogenesis through analysis of 3'UTR regions.

Results: An OpenArray platform (TaqMan® OpenArray® Genotyping System) was used for the case-control analysis of TS patients (N=564) and healthy controls. Starting from a list of candidate genes previously indicated as possible risk factors for TS, we screened for presence of SNPs in the 3'UTR regulatory regions. This analysis (data retrieved by mirSNP and polymiRTS databases) led to the identification of 32 SNPs which were predicted to change the seed sequence of in silico proposed miRNAs. To proof this concept, we performed functional validation study using a luciferase assay reporter containing 3' UTR regions of CHRNA7 and NTN4 transfected with their predicted miRNA. Specifically, miRNA-106b and miRNA-198b were identified as the most potent miRNA candidates for regulation of CHRNA7 and NTN4 gene expression. SKNF1 and HEK human cell lines were co-transfected using lipofectamine with the luciferase reporter-3' UTR construct of CHRNA7 and NTN4 (SwitchGear Genomics) and the corresponding putative miRNAs (miR-106b, miR-198b) along with non-targeting control miRNAs (miR-196b, miR-641b) in the functional validation studies.

Discussion: In order to increase our understanding of the underlying genetic and epigenetic mechanisms of TS, we aimed to study the possible miRNA regulation processes in TS-related genes, which would help not only to better understand the full genetic architecture of this disorder but also to determine how miRNAs contribute to the complexity of gene regulation in the development of disease.

OpenArray analysis identified significant differences among the selected candidates genes (LHX6, iMMP2L) confirming the implication of those genes in TS etiology. In the luciferase assays we characterized the regulatory effect of the predicted miRNAs on the expression candidate genes in a concentration-dependent manner, which showed up to 5-fold change in the relative gene expression levels in case of CHRNA7 and NTN4 thereby proving the concept of our study.

Disclosure

Nothing to Disclose.

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T36. GENOME-WIDE ASSOCIATION STUDY OF BORDERLINE PERSONALITY DISORDER REVEALS GENETIC OVERLAP WITH BIPOLAR DISORDER AND SCHIZOPHRENIA

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Background: Borderline personality disorder (BPD) is characterized by mood lability and impulsivity – symptoms which overlap with symptoms of Bipolar Disorder (BD) – a disorder showing a substantial comorbidity. Research suggests that its etiology involves both environmental and genetic factors. Formal genetic studies indicate a heritability of up to 65%. However, to date genetic research into BPD has been limited to candidate gene studies, and no case-control genome-wide association study (GWAS) has yet been performed. Systematic genome-wide screening for BPD personality features has been performed in individuals from the general population. Here, we present the first case-control GWAS of BPD, which was performed in one of the largest BPD patients samples worldwide. Given the heritability estimates for BPD, no significant single marker results were expected. Rather, we were interested in findings pointing to genes, gene-sets, and potential overlap with other psychiatric disorders.

Methods: GWAS was performed in 1,034 BPD patients and 1,545 controls recruited at four German academic institutions (Mannheim, Berlin, Mainz, Munich). After quality control and imputation, association was tested under an additive logistic regression model using PLINK and the derived principal components as covariates. Gene-based tests were performed

using VEGAS and MAGMA. Gene set analyses were performed with GSEA for GWAS using GO. Further gene set analyses are currently being performed. The LD regression score method was used to calculate genetic overlap between BPD, BD, and Schizophrenia (SCZ).

Results: The top hit of the SNP-based analysis was Developmental Pluripotency Associated 3 (DPPA3, p=1.65x10-7). The top hit of the gene-based analysis was Plakophilin4 (PKP4) which reached genome-wide significance using MAGMA (p=5.26x10-7). The gene set analysis also yielded a significant finding after correction for multiple testing, i.e., exocytosis (GO:0006887; p=0.001). The genetic correlation between BPD and BD was rg=0.34 (p=4.37x10-5), and that between BPD and SCZ was rg=0.28 (p=2.99x10-3).

Discussion: The present study is the first case-control GWAS of BPD. As expected, no significant association was found with any single marker or gene. The top SNP was in the gene DPPA3, which is implicated in epigenetic mechanisms. The top gene of the gene-based test – PKP4 – was also one of the top hits of the single marker analysis. PKP4 is involved in the regulation of cell adhesion and cytoskeletal organization, processes which have been linked to BD and SCZ. The most promising gene of the previously reported GWAS on BPD personality features - SERINC5 - showed nominally significant association. Previous research has implicated the top hit of the gene set analysis in the molecular mechanisms of BD and SCZ, and may now represent a promising starting point for further research into BPD.

The most interesting finding of the present study was the genetic overlap between BPD and BD as well SCZ. Our study is the first to demonstrate on the genetic level that BPD is not a discrete entity but overlaps with major psychoses not only on the clinical level. Future studies are warranted to determine commonalities and specificities.

Disclosure

Nothing to Disclose.

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T37. AN EXPANDED LATENT VARIABLE MODEL OF PSYCHOPATHOLOGY WITH HERITABILITY ESTIMATES

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Background: Solid evidence points towards dimensional conceptualizations of psychiatric disorders, emphasising the importance of latent factors to account for comorbidity among disorders and to provide additional clinical information to diagnostic thresholds. Therefore, continuous measures of psychopathology and factor analysis are high-potential in identifying latent sources of covariation among observed psychopathology. A consistent result from latent variable modeling studies is that two broad constructs underlie common DSM disorders: Internalizing and Externalizing. However, whether the inclusion of frequently overlooked disorders results in changes in the bi-factorial meta-structure and whether this structure is invariant across age and gender is often unclear. Finally, these phenotypic correlations indicate that disorders within the two spectra have similar etiologies. Estimating heritability and examining common genetic polymorphisms, like SNPs, provides an opportunity to quantify the shared genetic etiology of mental disorders.

Methods: The 7707 individuals (4084 women, 3623 men) included in the present study were selected from a sample of twins who participated in the Genetics of Sexuality and Aggression (GSA) project, launched in 2005 at the Abo Akademi University in Finland. In addition to indicators of anxiety, depression, psychopathy and alcohol use, our factorial structure included measures of eating attitudes, body image, sexual functioning, anger and aggression. We carried out a series of exploratory factor analyses to estimate measurement models, testing our hypothesis about the number of underlying factors. The results of these analyses were used to develop confirmatory factor analyses and validate the relations between the scales and the emerged latent constructs. To clarify whether the factor structures were equivalent across gender and age, measurement and structural invariance tests were performed. Genotype data are available for estimating heritability (ongoing).

Results: Measures of psychopathy, aggression, anger and alcohol abuse loaded on a first factor, interpreted as Externalizing; depression, anxiety and sexual distress indicators loaded on a second, Internalizing factor; eating attitudes and body image scales created a third factor we named Body. This three-factor model showed significantly better fit compared to a two-factor and a one-factor models. However, the two factor model where body-related problems loaded onto Internalizing also showed acceptable fit, consistent with the existence of two main dimensions of psychopathology. Both models were valid for women and men, although levels of specific indicators differed across genders, determining differences in factor means. Models were not equivalent across generations.

Discussion: We investigated latent dimensions, rather than psychiatric categories, to understand pathological patterns and to elucidate how disorders interact in shaping the structure of psychopathology. We expanded the Internalizing-Externalizing meta-structure and highlighted a novel spectra of Body-related disorders, but our data still suggests that comorbidity between mental disorders is largely accounted for by two broad latent dimensions. Based one the GSA data, we are currently carrying out an extended twin family study with Single Nucleotide Polymorphisms. Heritability estimates will be presented at the Congress.

Disclosure

Nothing to Disclose.

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T38. PRELIMINARY MODEL FOR THE GENETIC PREDICTION OF CLOZAPINE RESPONSE

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Background: Despite its clinical utility, the antipsychotic clozapine (CLZ) has not yet had a promising pharmacogenetic test developed for prediction of response. In the past 20 years, multiple genetic variants (e.g. dopamine, serotonin) have been suggested to be associated with CLZ response. Arranz et al (2000) proposed a model to predict response, but it was not replicated in independent samples. Since then, no other studies have sought to create a genetic panel predicting response to CLZ. Thus, we reinitiated the effort to develop a genetic model for CLZ response incorporating the most promising findings from our group's repository of CLZ response studies.
Methods: Our sample consisted of 151 Caucasian subjects with schizophrenia (SCZ) (DSM-III) treated with CLZ for six months. Response was assessed using the Brief Psychiatric Rating Scale (BPRS), and evaluated using absolute score change and binary response (Kane et al. 1988 criteria), with baseline score as a covariate. A total of 99 polymorphisms were tested from a range of candidate genes. Variants showing at least a nominal statistical trend ($p<0.1$) were included in the model. An unweighted risk score was calculated for each SNP and assessed for association with response. Five-fold cross validation was performed in an attempt to limit model overfitting. The model was then tested in an independent sample of antipsychotic-treated SCZ patients of European ancestry (CATIE subsample, $N=390$) to examine generalizability of findings to other antipsychotics.
Results: Four markers from genes encoding for dopamine D2 receptor (DRD2), serotonin-6 receptor (5-HT6), brain-derived neurotrophic factor (BDNF), and neurexin-1 (NRXN1) were included in the model. We observed a statistically significant association between genetic risk score with BPRS score change ($p=0.000039$, Adjusted $\hat{R}2=0.565$) and binary response ($p=0.004$, Nagelkerke $\hat{R}2=0.097$) assuming a linear increase in response for each additional risk allele. The model had an accuracy of 62%, a sensitivity of 70%, and a specificity of 47%. The model was not significantly associated with response in the independent CATIE European Caucasian subsample treated with other antipsychotics ($p=0.10$).
Discussion: We have developed a preliminary genetic model for CLZ response that includes genes with strong rationale for involvement. NRXN1 is a synaptic membrane cell-adhesion protein that has been suggested to modulate NMDA receptor activity, which is indirectly regulated by CLZ. The 5-HT6 receptor is involved in neurite growth and has lower expression in the hippocampus of SCZ patients compared to healthy controls. It mediates cognitive function, anxiety, and positive symptom improvement in animal models of SCZ.

The model does not appear to generalize to other antipsychotics. For CLZ response prediction per se, replication in independent studies of CLZ response in SCZ is required to confirm the validity of these findings.

Disclosure

Nothing to Disclose.

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T39. THE ROLE OF MICRORNAS IN THE COURSE OF SEVERE MENTAL DISORDERS

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Background: Illnesses from the schizophrenia-to-bipolar spectrum have a highly variable course. Determinants of these different individual trajectories have been of particular interest to scholars during the past century. Beyond rudimentary understanding, however, different course types have been difficult to delineate in categorical disease phenotypes. We have therefore embarked upon a project in which we seek to delineate different course types in a large longitudinal sample of deeply phenotyped patients suffering from disorders of the schizophrenia-to-bipolar continuum. With respect to biology, a dysregulation of microRNAs, small non-coding RNA molecules that flexibly influence transcription, in mental disorders is increasingly recognized. To combine both of these novel approaches, we plan investigate the role of microRNAs in different course types identified using longitudinal cluster analysis.
Methods Longitudinal clustering: Participants were selected from an ongoing longitudinal, multi-site study (www.kfo241.de, www.PsyCourse.de). Patients with a

DSM-IV diagnosis of the schizophrenia-to-bipolar spectrum were comprehensively phenotyped at four time-points over a period of 18 months. A set of longitudinally measured variables on current psychopathology, medication adherence, substance use, cognitive performance, level of psychosocial functioning and various questionnaires was analyzed using factor analysis for mixed data followed by longitudinal cluster analyses. This resulted in the identification of distinct subpopulations of patients, each being heterogeneous in terms of diagnostic composition.

MicroRNA sequencing

So far, we have compared four different methods to isolate blood borne small non-coding RNAs for RNA-sequencing. By this we were able to establish SOPs for the reliable analysis of circulating small non-coding RNAs in longitudinal cohorts.

Results: We will present results of our research project at the meeting.

Discussion: We will discuss our research project at the meeting.

Disclosure

Nothing to Disclose.

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T40. REPLICATION STUDY OF GWAS AND OTHER STRONGLY ASSOCIATED MARKERS FROM CHROMOSOME 6 IN NORTH INDIAN POPULATION

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Background: Schizophrenia is a polygenic neuropsychiatric disorder wherein specific molecular or phenotypic markers have not been reported, with several promising findings but inconsistent replication. Nevertheless, different markers from chromosome 6, discussed repeatedly and reinforced by GWAS findings, remain the most promising leads. The present study was carried out to replicate the important GWAS findings ($p < \text{or} = 10\text{-}8$) in a modestly sized case and control sample from a North Indian population

Methods: Schizophrenia cases (n=1035) and matched healthy controls (n=1035) were recruited at PGIMER-Dr.R.M.L. hospital. Controls included age and gender matched psychiatrically healthy adults and cord blood samples. Using Sequenome platform, 26 markers were evaluated.

In a subset of the samples (n=173 cases; n=87 controls), 8 different cognitive domains were evaluated using the UPenn Computerized Neuropsychological Battery, for the markers.

Results: Three markers namely rs2064430 (p=0.04, OR= 1.14, CI=1.01-1.3, AHI), rs6932590 (p=0.05, OR= 0.85, CI=0.73-1.00, intergenic), rs6916921 (p=0.05,OR=1.19, CI=1.00-1.43, NFKBIL1) showed modest association to DSM IV schizophrenia diagnosis under allelic test of association while rs3130615 and rs6916394 showed genotypic (p=0.04, p=0.02) and recessive association (p=0.01, 0.05) but none withstood Bonferroni correction. The most significant 2 marker haplotype using PLINK sliding window came from four regions: 1) intergenic region -rs6932590|rs3800318 (TA, p=0.02) 2) HLADQA1 region- rs377763|rs9273012 (GA, p=0.04) and 3) TNF region-rs1800610|rs986475 (CC, p=0.03) 4) MICB region- rs3130615|rs2516489 (CG, p=0.04). Significant association was observed among cases for rs377763 (p = 1.54*10-6) with 'Sensorimotor functioning' domain of the battery.

Discussion: The present study, although reaffirms association of a few chromosome 6 markers to schizophrenia in this ethnically distinct North Indian population; was of far lower magnitude than p=10-8 seen in initial GWAS findings.

Disclosure

Nothing to Disclose.

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T41. DISSECTING RELIGIOUS DELUSIONS IN SCHIZOPHRENIA: THE INTERPLAY OF RELIGIOUS ACTIVITY AND POLYGENIC BURDEN

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Background: Religious delusions are common symptoms in patients experiencing psychosis. They have been associated with greater severity of illness. However, the prevalence of religious delusions varies considerably between different cultures and societies. To enhance our knowledge of this distinct psychotic feature, we investigated if genetic and/or environmental factors were associated with the occurrence of religious delusions.
Methods: We studied 271 adult German patients with schizophrenia or schizoaffective disorder diagnosed according to DSM-IV criteria. For 196 of these patients, we were able to calculate PGC- schizophrenia polygenic risk scores (PGC-SZ-PRS). Polygenic risk scores reflect the cumulative burden of risk alleles carried by an individual according to the well-powered genome-wide association study (GWAS) investigated by the Psychiatric Genomics Consortium (PGC). Association of variables with a lifetime occurrence of religious delusions was tested by multiple logistic regression with occurrence of religious delusions being the binary target. The following variables were considered as putative predictors: self-reported degree of religious activity, DSM-IV diagnosis, sex, age, education level, marital status, presence of acute delusion at the time of interview and the PGC-SZ-PRS.
Results: Of the 271 patients (217 Christian, 9 Muslim, 45 without religious denomination), 102 (38%) experienced religious delusions during illness episodes. Neither declaring a religious denomination nor the self-reported degree of religious activity differed between subjects who were acutely versus not acutely delusional at the time of interview. The risk of experiencing religious delusions was significantly increased in individuals with a strong religious activity compared to subjects without a religious denomination (OR 3.3, p= 0.014). Low or moderate religious activity had no significant effect. None of the other covariates (DSM-diagnosis, sex, age, school education, marital status, acute delusion at the time of interview) were significantly associated with the lifetime occurrence of religious delusions. The same analysis including only 196 subjects for whom SZ-PRS score were available revealed the same effect of high religious activity on occurrence of religious delusions (OR 3.0, p=0.047). In these patients, the risk of experiencing religious delusions was also higher when the PGC-SZ-PRS increased by one sample standard deviation (OR 1.5, p=0.025).
Discussion: Our results suggest that the occurrence of religious delusions in schizophrenia and schizoaffective disorders is associated with environmental as well as genetic influences. Our data imply that high religious activity and a high SZ-PRS are largely independent liability factors. In conclusion, religious delusions may typically be seen in patients with a high degree of religious activity and/or a high polygenic burden of schizophrenia risk alleles. Moderate religious activity seemed to have no negative effect and may even be helpful for coping with these disorders.

Disclosure

Nothing to Disclose.

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T42. ASSESSING GENETIC CONTROL OVER BRAIN MORPHOLOGY VARIANCE IN PSYCHOSIS: A GENOME-WIDE VARIANCE-CONTROLING QTL (VQTL) NEUROIMAGING STUDY

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Background: Most imaging genetic studies on psychosis have relied upon conventional quantitative trait locus (QTL) analysis, which examines whether distinct allelic variants in a DNA locus are associated with the mean difference in the quantitative measure of a phenotypic trait, e.g. mean brain volumes.

However, alternative genotypes can also moderate the variance heterogeneity of a phenotype, which is frequently referred to as variance-controlling QTL (vQTL). This type of genetic control has been observed across several species and traits, and is usually associated to genetic sensitivity to environmental fluctuation. This is highly relevant for an application in imaging genetics in light of the influential diathesis-stress model of psychopathology. To the best of our knowledge, no previous study has evaluated the presence of vQTLs for brain morphology.
Methods: Participants: The sample analyzed so far consists of 504 individuals recruited through the ongoing Thematically Organized Psychosis (TOP) study, which includes 216 healthy controls (HC), and 288 patients with psychosis (SZ: 143, BD: 145). Patients were diagnosed using the structured clinical interview for DSM-IV (SCID) by trained clinicians.

Genetic data: The participants were genotyped with the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix Inc, Santa Clara, CA, USA). Quality control was performed using PLINK.

Brain imaging: Magnetic resonance imaging (MRI) structural data were acquired using a 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence, and the T1-weighted scans were processed using FreeSurfer, to obtain estimated of cortical thickness/area/volume and subcortical volumes.

vQTL assessment: The relationship between genome-wide single nucleotide polymorphism (SNP) variants and the phenotypic variance of each brain feature of interest was assessed by means of double generalized linear models, and multiple testing adjustments were later performed.
Results: Exploratory analyses revealed no significant between-group differences in variance for the brain features considered. Genome-wide vQTL analyses indicated that the population variance of features such as cerebellar volume and temporal pole cortical thickness could be under partial genetic control. Replication of these findings and

diagnose-genotype interaction tests are currently being implemented and are expected to be competed by early autumn 2016.

Discussion: The findings suggest that inter-individual variability in brain morphometry may be influenced by specific genetic variants. Carriers of those genotypes may be particularly susceptible to brain deficits and psychopathology after exposure to pathogenic environments and, simultaneously, have increased likelihood of benefiting from enriched/non-adverse experiences.

Disclosure

Nothing to Disclose.

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T43. GENOME-WIDE ASSOCIATION OF TARDIVE DYSKINESIA: PRELIMINARY FINDINGS

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Background: Tardive dyskinesia (TD) is a movement disorder manifested as involuntary movement of orofacial muscles or choreoathetoid movements of trunk and limbs. Commonly observed in schizophrenia, TD is potentially a persistent and irreversible condition associated with sustained antipsychotic treatment. While various theories have been put forth, the pathophysiology of TD is still unclear, with no well-accepted treatment. The occurrence of TD in only some patients appears to suggest possible individual genetic susceptibly. Recent genome-wide association studies (GWAS) have identified several candidate genes such as the GLI2 and HSPG2, however, none of these candidate genes were identical to those from candidate gene studies. Here, we performed a GWAS on TD schizophrenia patients of Chinese ethnicity.

Methods: The sample consisted of 842 schizophrenia patients of Chinese ethnicity, recruited from the Institute of Mental Health Singapore. Diagnosis of schizophrenia was ascertained on the Structured Clinical Interview for DSM-IV, and dyskinesia was rated on the Abnormal Involuntary Movement Scale (AIMS). Genotyping was performed using the Illumina 1M Duo Beadchip. Standard GWAS QC procedures were carried out. QC-ed markers were phased with SHAPEIT and imputed via Minimac3 (MACH) to the 1000 Genomes Project Phase 3 reference panel (GRch37). Subsequent association tests were conducted on PLINK2.

Results: None of the markers reached genome-wide significance. One-hundred top SNPs (top SNP: rs55823922, Rsq = 0.999, MAF = 0.241, Beta = 0.244, SE= 0.0485, p = 6.323x10-07) were identified. The genes in closest proximity to top SNPs are P2RY1 (purinergic receptor P2Y1), RAP2B (RAS protein 2B) and MBNL1 (Muscleblind like splicing regulator 1).

Discussion: None of the genes associated with TD were implicated in psychiatric conditions. The purinergic receptor 1 protein functions as a receptor for extracellular adenine nucleotides, and mediates adenosine diphosphate (ADP) induced intracellular calcium mobilisation in platelet binding; it is implicated in Alzheimer's disease. The RAP2B is involved in cell growth, differentiation, and apoptosis, and is implicated in the Epidermal Growth Factor Receptor and Cholinergic Signalling pathways. MBNL1 is a member of the muscleblind protein family which has been implicated in myotonic dystrophy, a condition characterised by muscle abnormalities and muscle wasting. These susceptibility genes appear to be involved in neurodegenerative conditions, and are congruent with the neurodegenerative theory of TD. Further replication is warranted.

Disclosure

Nothing to Disclose.

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T44. IS LANGUAGE IMPAIRMENT IN SCHIZOPHRENIA RELATED TO LANGUAGE GENES?

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Background: Schizophrenia is considered a language related human specific disease. FOXP2 and CNTNAP2 are genes that have been related to language abnormalities; with FOXP2 additionally showing association with schizophrenia in a limited number of studies. In this study we investigated whether FOXP2 and CNTNAP2 are associated with a) severity of formal thought disorder (FTD) – a core language symptom present in schizophrenia, and b) animal fluency scores – a core language production deficit in schizophrenia; where patients have reduced performance.
Methods: Genotyping for FOXP2 and CNTNAP2 was completed at rs17137124 and rs7794745. Comprehensive clinical interviews and fluency testing using the one minute animal fluency tests were obtained from 53 schizophrenia patients and 119 healthy controls. Fluency scores representing the number of unique animals delivered in one minute. Formal thought disorder was measured using the Thought, Language and Communication scale with scores ranging from 0 to 4.
Results: Schizophrenia T-allele carriers (TC & TT) of FOXP2 rs17137124 had reduced fluency (animals) compared to: a) healthy controls and b) compared to CC schizophrenia homozygotes (p=.005): SZ (CC= 23.8, TC=18.4, TT= 13.7) and HC (CC=23.8, TC=24.3, TT=24.9). Further, schizophrenia T-allele carriers had increased FTD (p=.046) (CC=1.8, TC=3.1, TT=3.2). T-allele carriers (TA & TT) of CNTNAP2 rs7794745 in the schizophrenia cohort had reduced semantic fluency: schizophrenia (AA= 19.5, TA=18.8 and TT= 15.7) and health controls (AA=24.7, TA=25.0 and TT=25.0), and increased FTD (AA= 1.2, TA=2.7 and TT= 3.5) although neither of these later two analyses reached significance (p=0.1). The CNTNAP2 result possibly being due to very uneven group sizes, with a small TT group (Ns: AA=17, TA=30 and TT=6). Data collection is continuing.
Discussion: These preliminary results suggest that genes that have been related to receptive and expressive language skills in healthy humans are associated with common language symptoms in schizophrenia: the FOXP2 gene being highly significant with regards to this association. Given our poor understanding of the aetiology of specific symptoms in schizophrenia this work offers a substantial advance in the field; in addition to improving of understanding of the genetics of language more generally.

Disclosure

Nothing to Disclose.

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T45. GENETIC FACTOR COMMON TO SCHIZOPHRENIA AND HIV INFECTION IS ASSOCIATED WITH RISKY SEXUAL BEHAVIOR

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Background: The relationship between schizophrenia (SZ) and human immunodeficiency virus (HIV) infection is complicated epidemiologically and genetically. Although observational studies have described their co-occurrence and their joint relationship with risky sexual behavior (RSB), their genetic correlations are not well studied.
Methods: We performed an extensive search for genetic factors common to SZ and HIV using publically accessible summary statistics from genome-wide association studies of HIV infection and schizophrenia. To study the relationship of these disorders with risky sexual behavior (RSB), 2379 European Americans were genotyped and assessed for RSB score using the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA). Genetic relationships between traits were analyzed in three ways: linkage disequilibrium (LD) score regression to estimate genetic correlation; GPA (Genetic analysis incorporating Pleiotropy and Annotation) to test pleiotropy and identify pleiotropic loci; and polygenic risk scores (PRS) for SZ and HIV to predict RSB using linear regression. Bipolar disorder, height and body mass index (BMI) were tested as negative controls.
Results: We found that SZ and HIV have a positive genetic correlation, which is highly significant both with (cor=0.2, p=0.001) and without (cor=0.17, p=0.002) inclusion of the MHC region. Consistently, our pleiotropy analysis (p=5.31E-28) showed that a majority of the shared genetic variants have the same effect direction (shared-effect pleiotropic SNPs), meaning that the same allele tends to increase or decrease the risk of both SZ and HIV. Pleiotropic SNPs that influence schizophrenia and HIV infection with the same effect direction (shared) were enriched for chromatin assembly (p=1.3E-9) nucleosome organization (p=4.4E-9), and protein-DNA complex assembly (p=1.8E-8). SNPs with opposite effect directions (antagonistic) were enriched for the regulation of synaptic transmission (p=8.2E-6) and neurotransmitter transport (p=5.5E-5), neuronal differentiation (p=3.8E-5), and the regulation of nerve impulse transmission (p=2.4E-5). SZ PRS

computed with antagonistically pleiotropic SNPs significantly predicted RSB score (p=0.019), but SZ PRS based on either shared pleiotropic SNPs or all SNPs did not predict RSB.

Discussion: The epidemiologic correlation between schizophrenia and HIV can partly be explained by overlapping genetic risk factors, which are related to risky sexual behavior. These findings call for further study of these SNP sets, and when available, using genetic risk scores from them to test other phenotypes that could yield important insights into these very serious disorders and behaviors associated with them.

Disclosure

Nothing to Disclose.

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T46. IN VITRO HUMAN NEURONAL DIFFERENTIATION VALIDATED AS GENOMIC MODEL SYSTEM TO STUDY MAJOR PSYCHIATRIC ILLNESSES

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Background: Large-scale genetic studies of neuropsychiatric disorders have identified hundreds of susceptibility alleles. An important next challenge is to understand how identified genetic risk loci impact biological pathways and disease. For this, model systems are needed that recapitulate biological pathways in cell types that align with etiological mechanisms underlying the disease. We therefore aim to investigate an in vitro model of neuronal differentiation using human neural stem cells (hNSC) and evaluate its potential for studying molecular pathways important for major psychiatric illnesses based on genome-wide disease risk identified through GWAS.

Methods: We differentiated WA09, a widely used hNSC line with standardized lab protocols, to a neuronal lineage across 30 days and assayed genome-wide gene expression profiles at seven time points in at least triplicates. We first used transition mapping (TMAP) together with publicly available brain transcriptome datasets to investigate overlap in transcriptional profiles between in vitro neuronal differentiation and in vivo human brain development. We furthermore setup a statistical pipeline tailored to time-series expression data that identifies genes with non-constant expression over time and subsequently performs soft clustering according to similarity in expression patterns using an empirical Bayes approach and fuzzy c-means clustering, respectively. We next applied stratified LD score regression, a statistical method that partitions heritability from GWAS summary statistics, to estimate how each unique identified cluster contributes to heritability of major psychiatric illnesses using results statistics of large GWAS (>5,000).

Results: We first show that in vitro transcriptional profiles significantly match in vivo human neurodevelopmental stages and cellular laminae of human cortical regions, which emphasizes the relevance of this model for studying brain function. We identified >30% of genes to be differentially expressed with high probability. These genes are important for in vitro neuronal differentiation and group to 10 clusters with distinct expression patterns. Biological annotation of these clusters highlights pathways and mechanisms important for neuronal differentiation, such as transcription factor activity, RNA processing, and synaptic transmission. Finally we show that differentially expressed genes are significantly enriched for heritability of schizophrenia, bipolar disorder, and major depressive disorder. There is no enrichment for height and Alzheimer's disease, which is a late onset neurodegenerative disease. The enriched heritability partitions into specific clusters that can be distinct or shared between the three disorders with the strongest signal for schizophrenia in a cluster that contains genes related to synaptic function and transmission.

Discussion: In summary, we present an in vitro model of neuronal differentiation that at baseline activity shows overlap in transcriptional profiles with human cortical development. These profiles are enriched for genome-wide disease risk of major psychiatric diseases that partitions to specific identified gene clusters. This functional model is robust and simple and allows for genomic manipulations across an isogenic background in a controlled environment. This study validates WA09 neuronal differentiation as an in vitro genomic tool to study major psychiatric illnesses and provides directions for GWAS functional follow-up studies.

Disclosure

Nothing to Disclose.

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T47. FKBP5 EPIGENETIC CHANGES IN SCHIZOPHRENIA: SIMILARITY TO STRESS-RELATED CONDITIONS

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Background: Hypothalamic–pituitary–adrenal (HPA) axis dysregulation is a potential neurobiological mechanism proposed by vulnerability-stress model for schizophrenia. Recent studies highlighted the role of functional genetic variants of FKBP5 gene, which affect the activity of HPA axis

following stress exposure, and supported the hypothesis of increased stress sensitivity in schizophrenia. Additionally, FKBP5 demethylation in Intron 7 was observed in stress-related conditions thus the purpose of this pilot study was to investigate FKBP5 methylation levels at Intron 7 in schizophrenia.

Methods: Ethnically homogeneous Serbian sample of 24 schizophrenia spectrum patients and 24 controls matched by age and gender with patients' group, were analyzed regarding DNA methylation levels at three CpG sites and average methylation level in Intron 7. Accordingly, we covered the area of GRE that has been reported to be associated with altered stress responsiveness. Epigenetic changes in FKBP5 Intron 7 were measured by Sanger sequencing and compared between the groups using t test as appropriate.

Results: Analyses revealed decreased FKBP5 methylation at the three targeted CpG sites (CpG1, CpG2, and CpG3) in patients compared to controls ($p=0.026$, $p=0.017$, and $p=0.027$, respectively). Similarly, when we averaged methylation scores of the observed region in Intron 7, significant demethylation was detected in patients ($p=0.003$).

Discussion: To the best of our knowledge this is the first study which explored FKBP5 epigenetic changes in schizophrenia. Conclusively to previous stress-related conditions, our preliminary results revealed significant decrease of FKBP5 methylation levels in Intron 7 in patients with schizophrenia. FKBP5 demethylation presents further insight into the reported FKBP5 genetic influence in psychosis and could be promising terapeutic target for the prevention of the onset and the course of schizophrenia.

Disclosure

Nothing to Disclose.

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T48. MOLECULE-BASED GENETIC ASSOCIATION STUDIES ON PSYCHIATRIC DISORDERS

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Background: GWAS have successfully detected genetic variants associated with schizophrenia [Ripke et al., 2014]. However, only a small fraction of heritability can be explained. Gene-set/pathway based methods can overcome limitations arising from single SNP-based analysis, but most of them place constraints on size which may exclude highly specific and functional sets [Ramanan et al., 2012], like macromolecules. Ion channels, belonging to macromolecules, are created by polymerization of several subunits whose encoding genes are located far away or even on different chromosomes. We combined such molecules information with GWAS genotype data to investigate how functional channels associated with psychiatric disorders.

Methods: We defined a biologically meaningful gene-set based on channel structure and performed association study applying the SNP-set (Sequence) Kernel Association Test [Wu et al., 2010] to the Psychiatric Genomics Consortium (PGC) genotype data from bipolar disorder and schizophrenia.

Results: In the first stage of study (Voltage-gated calcium (Cav) channels vs schizophrenia), we identified 8 out 9 subtypes of Cav channels significantly associated with schizophrenia, including the L-type channels (Cav1.1, Cav1.2, Cav1.3), P-/Q-type Cav2.1, N-type Cav2.2, R-type Cav2.3, T-type Cav3.1 and Cav3.3. Only genes from Cav1.2 and Cav3.3 have been implicated by the largest GWAS ($N = 82,315$). In the second stage of study, more ion channels (K+ channels, Na+ channels, ...) have been analyzed and data from bipolar disorder was investigated. The results will be presented.

Discussion: The results suggest that abnormalities of Cav channels may play an important role in the pathophysiology of schizophrenia. Analyzing subunit-encoding genes of a macromolecule in aggregate is a more powerful approach to identify the genetic architecture of polygenic diseases. Molecule-based genetic association study offers the potential of power for discovery and natural connections to biological mechanisms of psychiatric disorders. Significant channels may represent appropriate drug targets for therapeutics.

Disclosure

Nothing to Disclose.

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T49. COMORBIDITY OF MULTIPLE-FACTOR AND HEREDITARY DISEASES IN FAMILIES: CONTRIBUTION TO SCHIZOPHRENIA GENETICS

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Background: The comparative role of heredity in the etiology of schizophrenic disorders is estimated as 60-70%, other 30-40% is the share of the environment. However, modern molecular-genetic technologies, including full-genomic, are not able to explain more than 10-15% of the general hereditary components of this multiple-factor

disease. One of the main resources of disclosing "missing heritability" is connected with the schizophrenia phenotype, study of clinical polymorphism of schizophrenia and comorbid with it hereditary diseases.

Methods: For 209 families of patients with different forms of schizophrenia (F20 according to ICD-10) by means of the genealogical method family trees with identification of state of mental and physical health of relatives of the first degree of relationship were made. If hereditary diseases being suspected, biochemical investigations with identification of metabolites, molecular-genetic (with testing of genetic polymorphisms) investigations were carried out.

Results: Identification of the role of genetic factors in developing of diseases of the noninfectious nature to which schizophrenic disorders belong, through detection of associations of such diseases with Mendelian characters in families showed the following. Schizophrenia and hereditary Mendelian recessive disease with disturbance of the gene coding Cu-transporting ATPase - Wilson-Konovalov illness (hepatocerebral dystrophy). Schizophrenia and hereditary Mendelian dominant disease (with complete penetrance and varying expressivity of the gene FBN1 (fibrillin 1) - the peculiar Mass-phenotype of the proband and his relatives in the area of the father. Schizophrenia and Leiden mutation (predisposition to thrombosis, thrombophilia) with molecular-genetic investigation of polymorphism of Arg506Gln in the gene of V factor of coagulation. The heterozygotic carriage (G/A genotype) was found. Schizophrenia with manifestations of the velocardiofacial syndrome and existence of polymorphisms of alleles of Val 158Met and rs4680 of the gene COMT as well as CYP2D6 gene polymorphisms.

Discussion: For schizophrenic disorders as diseases with family history and blunted phenotype which do not conform Mendelian patterns of inheritance in which complex interaction of many pathogenic genes with environmental factors takes place, identification of comorbid with them hereditary (chromosomal and gene) diseases gives the chance of the differentiated clinical diagnostics, prediction of course and development, treatment and outcome of the disease for the specific patient as well as possibility of primary prevention in families.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.537

T50. LONGITUDINAL EPIGENETIC ANALYSIS OF CLOZAPINE USE IN TREATMENT-RESISTANT SCHIZOPHRENIA: DATA FROM THE CRESTAR CONSORTIUM

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Background: Approximately one-third of patients with schizophrenia are considered treatment-resistant. For these patients, the atypical antipsychotic drug clozapine is recommended as the only evidence based treatment available. However, there is still significant variability in treatment-response. Animal studies have demonstrated that clozapine influences histone modification and DNA methylation, and a recent EWAS study in humans identified multiple differentially methylated positions (DMPs) and differentially methylated regions (DMRs) in clozapine-exposed samples. We used a longitudinal, within-participant design to conduct genome-wide analysis of DNA methylation changes in treatment resistant patients over 6 months of clozapine use.

Methods: We recruited 20 participants with a diagnosis of treatment-resistant schizophrenia, before they were prescribed clozapine. We then collected whole-blood samples at baseline and follow-up (6 weeks, 12 weeks and 6 months after clozapine start date), alongside clinical assessments. We quantified DNA methylation at $\sim$ 480,000 sites across the genome using the Illumina 450 K HumanMethylation array and following pre-processing, normalization and quality control, an epigenome-wide association study was performed comparing DNA methylation at each time point.

Results: Preliminary data demonstrates an overall reduction in DNA methylation in the 6 months of clozapine use, with multiple individual CpG sites showing changes in DNA methylation that were found to be significantly associated with length of time exposed to clozapine. During analysis of the first 10 patients, the most significant CpG site was located in the gene body of CRB1; CRB1 is expressed exclusively in the eye, and the central nervous system, and has been previously associated with Lever's congenital amaurosis and retinitis pigmentosa. The findings and

analysis for all 20 participants will be presented at the meeting.

Discussion: This is the first study to identify longitudinal epigenetic changes following clozapine exposure in human subjects, replicating findings in animal studies of decreased methylation. Recruitment is ongoing and further analysis will look at whether epigenetic changes are associated with treatment-response/adverse reactions. Ultimately, these data will help us understand the mechanisms involved in clozapine, potentially providing biomarkers to predict clozapine response.

Disclosure

Nothing to Disclose.

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T51. USING MACHINE LEARNING TO BUILD INDIVIDUALIZED PREDICTION MODELS OF FUTURE QUALITY OF LIFE IN PSYCHOSIS PATIENTS

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Background: Schizophrenia (SCZ), bipolar disorder (BD) and schizoaffective disorder (SCZA) are severe, chronic mental illnesses, characterized by a marked decrease in quality of life (QoL) and functioning in a great proportion of patients. QoL, subjective well-being and psychosocial functioning are important determinants of patient satisfaction and patient-physician relationship and improvement in these domains is often more important for the patients than the reduction of clinical symptoms. With the growing emphasis on personalized care in everyday clinical practice, there is an increasing need for tools that can provide individual predictions on the future course of these patient-centered domains and thus help clinicians in providing individually tailored interventions. Therefore, we used machine learning to predict general and psychological QoL 6-months after an initial assessment in individuals diagnosed with SCZ, BD and SCZA using a combination of clinical, demographic and genetic variables.

Methods: In an ongoing longitudinal naturalistic study (www.kfo241.de, www.PsyCourse.de), patients meeting DSM-IV criteria for BD, SCZ and SCZA were recruited at multiple sites across Germany and Austria. Information on their sociodemographic background, family history, current psychiatric symptoms, functioning and QoL (WHOQoL-BREF) was obtained with a battery of rating scales in 6-month intervals. For the current analysis results of T1 (N=764) and T2 (N=428) were used.

Participants were genotyped on the PsychChip (Illumina) whole-genome SNP array and their SCZ polygenic risk scores (PRS) at 11 different p-value thresholds (pTs) (pT1=0.00000005, pT11=1) were calculated using data from SCZ PGC2 (excluding German participants) as training data set. The importance of the clinical and demographic features and the cumulative SCZ polygenic risk in predicting 6-month (T2) general and psychological QoL was tested using linear Support Vector Machines. The prediction algorithm was wrapped into a repeated-nested cross-validation setting to ensure good generalizability.

Results: Higher baseline scores on the negative symptoms subscale of the PANSS, higher levels of baseline depression (BDI), lower level of functioning (GAF) and being unemployed or having a part-time job were the most important determinants of impaired T2 general or psychological QoL (test-fold balanced accuracy 61.2% and 71.3%, respectively). The PANSS negative symptoms subscale items were more important in the prediction of general QoL, whereas items of the BDI depression scale had higher weight in predicting psychological QoL. Though having higher SCZ-PRS were associated with lower T2 general QoL, compared to the clinical variables, the SCZ polygenic risk seemed to play a less important role in determining future QoL and thus was not included in the final prediction model.

Discussion: Our results indicate that prognostic tools using clinical data can potentially be used to indicate future general and psychological QoL of SCZ, BD and SCZA patients. However, the predictive accuracy requires improvement to be clinically useful. Further research will investigate the association found here between SCZ-PRS and lower general QoL with more sensitive biological markers. Specifically, we are currently working on techniques which would allow us to add further genomic or transcriptomic data to the analysis.

Disclosure

Nothing to Disclose.

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T52. THE POTENTIAL ROLE OF LOW FREQUENCY AND RARE VARIANTS IN TARDIVE DYSKINESIA GENETICS

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Background: Tardive dyskinesia (TD) is a chronic, irreversible side effect of antipsychotic-treated schizophrenia patients TD occurrence is influenced by both clinical and demographic variables, as well as genetic factors. Contribution of common variants to TD susceptibility has been investigated in recent years, including by the genome-wide association study approach, but results are inconsistent. In order to discover the involvement of low frequency and rare variants in this phenotype, we implemented whole exome sequencing (WES) method.
Methods: We whole exome sequenced 20 Ashkenazi Jewish schizophrenia patients with severe TD, and 18 patients without any manifestation of TD (total AIMS score of zero) despite more than 10 years of exposure to antipsychotics. For prioritization, we concentrated on Loss of Function (LoF) rare variants.
Results: We were able to identify several interesting rare (1%-5%) and extremely rare (<1%) LoF variants which are possibly related to TD susceptibility and are biologically plausible. Follow-up case-control association study in a larger Jewish TD sample is needed to confirm these results. In addition, we identified extremely rare patient-private mutations among individuals with severe TD, that seem to be enriched in several neuropharmacological pathways relevant to this disorder.
Discussion: WES may be implemented in pharmacogenetics studies of antipsychotics. Our preliminary results point to the role of low frequency and rare LoF variants in TD.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.540

T53. CASCADE TF-MIRNA-MRNA REGULATIONS IDENTIFIED BY CO-EXPRESSION NETWORK MODULES IN BRAINS OF PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Schizophrenia and bipolar disorder are complex mental disorders, with risks contributed by multiple genes. Recently, genome-wide systemic approaches have been used to reveal the associations of hundreds of SNPs with those disorders. Dysregulation of gene expression has been implied, but little is known about such regulation systems in the human brain. Several methods have been developed to achieve measurement of large-scale or multi-level data on interactions in biological systems. Additional biological regulators, such as transcriptional factors (TFs), enhancers, and microRNAs (miRNAs) binding information may help us to unveil the underlying regulatory mechanisms in the networks and suggest causal relationships.
Methods: We analyzed two data sets using brain tissues from 51 patients with schizophrenia or bipolar disorder and 24 healthy controls. We applied whole genome transcriptome profiling using Affymetrix Human Gene 1.0 ST Array (Affymetrix, Santa Clara, CA) and miRNA sequencing on the Illumina 1G Genome Analyzer. Using weighted gene co-expression network analysis, we integrated gene expression data of mRNA and miRNA from the same brain collections, built mRNA-miRNA co-expression networks and detected differentially expressed modules. In silico predicted binding relationships of TFs and miRNAs were used to validate the putative regulations suggested by co-expression patterns. Using SNP genotype data, expression quantitive trait loci (eQTL) and Network Edge Orienting (NEO) analysis, we resolved causal relationships among the regulators and their targets. We further validated the predicted regulations using RNA interference knockdown experimentally.
Results: We identified a module differentially expressed between cases and controls (p = 7.6e-4, FDR q = 0.01). This module were enriched for neuron differentiation (p = 4.8e-7, FDR q = 8.5e-4) and neuron development (p = 2.3e-5, FDR q

= 4.0e-2), and contained five miRNAs and 501 mRNA genes. Six TFs also served as hub genes in these modules (POU2F1, EPAS1, PAX6, ZNF423, SOX5 and SOX9). The co-expression-suggested regulatory relationships were consistent with the binding relationships predicted by databases. Focusing on those regulations containing TFs and miRNAs, we resolved a regulation cascade from SNP variants (rs16853832) to TF (POU2F1) to miRNA (hsa-mir-320e) to target genes (NR2E1) and ultimately, to disease risks.

Discussion: We revealed POU2F1 as a key regulator in a neuron differentiation/developmental module associated with disease, and revealed a putative cascade regulation effect. This study showed that we can utilize multi-dimensional data to construct co-expression networks. Causal relationships can be resolved among SNPs, regulatory molecules and their downstream target genes through data integration. Novel genes and their corresponding regulations underlying the disease risks could be revealed.

Disclosure

Nothing to Disclose.

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T54. BEPS - BERLIN PSYCHOSIS STUDY

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Background: Over the past decade, genome-wide association studies (GWAS) have provided fundamental insights into the genetic architecture of schizophrenia with the identification of more than 100 risk loci and the discovery that common and rare variants contribute to a very complex genetic predisposition. However, these ground-breaking discoveries come with the realisation that the identification of risk loci is merely the start of a long process towards meaningful biological understanding. To clarify how the identified risk loci actually drive the pathophysiology of schizophrenia, we want to combine successful GWAS strategies with costly imaging or even pharmacologic studies, in order to improve power with a genotype based recruiting process.

Methods: As a first step, we want to recruit a new large case-control sample comprising 2500 individuals with schizophrenia and 2500 healthy controls from Berlin, Germany. As a second step, we will calculate a variety of distinct genetic risk scores (GRS) for all participants and re-invite cases and controls with particularly high or low genetic risk profiles. These then will be evaluated with detailed, deep phenotyping strategies.

Results: Our pilot study comprises 82 cases with schizophrenia and 86 healthy controls. Parents and grandparents of our probands come from central Europe (n = 146) or Turkey (n = 14). The cases subsample reported disease related hospitalalization between 1 and 40 stays (MV = 4.02 ; SD = 5.58). Amongst the healthy controls no participant reported a lifetime or family history of schizophrenia or bipolar disorder. Age, gender and level of education differ significantly between the two subsamples. Patients were older (MVcases= 41.89 years, SDcases = 11.87 years, MVcontrols = 35.85 years, SDcontrols = 14.08 years, $p < .05$), more likely men ($p = .018$) and reported a lower level of school education (MVcases= 10.62 years, SDcases = 2.48 years, MVcontrols = 12.02 years, SDcontrols = 1.31 years, $p < .05$) than the healthy control subsample.

Discussion: The main goal of this study is to further assess the biological mechanisms of schizophrenia via combining big meta analyses of genome-wide analysis studies with costly imaging genetics or pharmacologic studies. In fact, this study will have the potential to overcome the scientific limitations of both approaches and thus, give answers to many open questions regarding the biological and epidemiological mechanisms underlying schizophrenia.

Our pilot data confirms formerly reported epidemiologic data. We hope to have received genotypic data till October for this pilot sample and to report first GWAS results.

The final total sample of 5000 participants will be contributed to the psychiatric genomics consortium for it's newest GWAS meta analyses. Based on our experience, BEPS will yield to approximately 10 new genome-wide significant genetic associations.

Disclosure

Nothing to Disclose.

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T55. THE GENETIC BASIS OF THE COMORBIDITY BETWEEN CANNABIS USE AND MAJOR DEPRESSION

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Background: While the prevalence of major depression is known to be elevated amongst cannabis users, the causes of

this comorbidity are not clear. Here we investigate the role of genetics in this relationship and identify genomic loci linked to these traits.
Methods: Using a sample of Mexican American extended families (n=1,284), we use variance decomposition methods to establish the degree of genetic correlation between cannabis use and major depression. Genome-wide univariate and bivariate linkage scans are conducted to localize the chromosomal regions influencing these traits and the comorbidity observed between them.
Results: Both major depression (h2=0.349, p=1.06x10-5, SE=0.100) and cannabis use (h2=0.614, p=1.00x10-6, SE=0.151) are heritable traits, and there is significant genetic correlation between the two (ρg=0.424, p=0.0364, SE=0.195). Genome-wide linkage scans identify a significant univariate linkage peak for major depression on chromosome 22 (LOD=3.144 at 2cM), with a suggestive peak for cannabis use on chromosome 21 (LOD=2.123 at 37cM). A significant pleiotropic linkage peak influencing both major depression and cannabis use was identified on chromosome 11, using a bivariate model (LOD=3.229 at 112cM). This location spans the NCAM1-TTC12-ANKK1-DRDR2 gene cluster. Follow-up of this pleiotropic signal provided tentative evidence implicating a rare SNP 20kb upstream of NCAM1 (s7932341); with peak-wide significant bivariate association with cannabis use and major depression (p=3.10x10-5).
Discussion: We show that genetic influences play an important role in the comorbidity between cannabis use and major depression.Specifically, we identify a pleiotropic locus on chromosome 11, spanning the NCAM1-TTC12-ANKK1-DRDR2 gene cluster, which has been previously implicated in both addiction and depression research.

Disclosure

Nothing to Disclose.

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T56. STUDIES OF ALCOHOL RELATED PHENOTYPES ACROSS HUMAN, MOUSE AND INVERTEBRATE MODELS

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Background: Genetic influences on alcohol dependence (AD) have been well established, with the heritability of AD as estimated in behavioral genetic studies ranging from 50-60%. However, robust genetic association signals in human studies of AD have been limited. As part of the VCU Alcohol Research Center, we use multiple model organism systems (C. Elegans, Drosophila, mouse, and rat) and human studies to advance our understanding of the genetic basis of alcohol related outcomes. Molecular responses to ethanol are likely to be shared across species because signaling mechanisms are evolutionarily conserved. As individual genes and gene networks are associated with ethanol response in model organisms, it is critical to understand their association with human alcohol related phenotypes. In this study we tested the effect of several gene sets identified through model organism research with a range of phenotypes hypothesized to be involved in alcohol-related outcomes in human studies.
Methods: All the sets and genes were tested using one of the two related software depending if the sample contains independent individuals (Plink set based analysis) or the sample has dependent individuals (Gskat). In all human samples we used imputed data if available. Plink uses algorithm based on significant pruned SNPs ($\hat{r}2=0.5$) at the threshold (p=0.05) keeping LD structure and permuting phenotype randomly between individuals. Gskat performs Family based association test for sets via GEE Kernel Machine score test. We used covariates same as in previous GWAS and other analyses for each of the samples.
Results: We find evidence that there is some evidence of association in human samples in all three considered gene sets and genes separately for some considered phenotypes. Max number of drinks was strongly associated with several genes in human samples. Externalizing phenotype also showed association with several genes across most human samples. Considering several human samples allows us more preciously determine gene structure affecting alcohol related phenotypes.
Discussion: In these analyses we tested gene sets with known association in mouse and invertebrate models for the association in human samples using alcohol related phenotypes in an effort to characterize similarities between human phenotypes and animal analogues. It is important to take into account the multiple pathways by which genes may exert an effect on alcohol problems in humans. Analogues between human and animal models will help with explaining the biological and functional reasons creating behavioral problems.

Disclosure

Nothing to Disclose.

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T57. KHAT ABUSE AS RISK FACTOR FOR DEVELOPMENT OF PSYCHOTIC SYMPTOMS IN TRAUMA PATIENTS. A FEASIBILITY STUDY FOR FURTHER GENETICO-EPIDEMIOLOGICAL STUDIES IN THE GGFRC, ETHIOPIA

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Background: The Jimma University in southwestern Ethiopia has a unique health and demographic surveillance system called „Gilgel Gibe Field Research Center" (GGFRC) with a catchment area of about 50.000 people. In this setting, we studied the effect of khat use as risk factor for the development and the stability of psychotic symptoms among young men in the community. Our aim was to validate pilot data by testing the hypothesis, whether objective biological data on khat abuse are related in a meaningful way to behavioral self-reports of study participants and psychiatric symptom presentation assessed by trained interviewers. We assumed that khat alkaloids in urine samples of respondents are related to a higher probability of psychotic symptom presentation, especially in the subgroup with high trauma load. Furthermore, we wanted to demonstrate the reliability and validity of research methods that are necessary for future genetic epidemiological studies, i.e. the validity and reliability of pharmacological screening tests as well as assessments performed by trained local interviewers.
Methods: In this prospective study, trained local interviewers screened a representative cohort of young men twice within a period of nine months (T1: dry season, N=852, T3: rainy season, N=693) to determine the presence and stability of distinct psychiatric symptoms (CIDI) and to assess traumatic experiences (LEC-5). As part of the screening, urine samples were collected and analyzed for khat alkaloids by immunoassay tests for amphetamine. In a clinical validation interview (T2, N=126) mental health specialist reassessed the psychiatric symptom presentation (BPRS) in a randomly selected subgroup of 126 individuals of those persons who had been screened at T1. The validation study took also urine of this subgroup in order to validate the urine screening by a more extensive analysis of khat alkaloids (HPLC).
Results: Our results on the association between biological objective data and information on psychiatric symptoms assessed by interviews were related in a meaningful way: The proportion of khat-related psychotic symptoms was highest among respondents with positive khat tests and with high trauma load. This tendency was strongest during rainy season (T3) where the market availability and the use of khat was higher (Chi2 = 14.800, df 1, $p < .001$). In a Binary Logistic Regression model we found a significant interaction effect of amphetamine test * trauma load (OR = 2.822, CI 95% 1.030 – 7.732, p = .044).
Discussion: By showing these meaningful variations, this pilot study suggest that important theories on the development of psychosis can be further studied in epidemiological and longitudinal designs among khat users. Our project can be seen as a pilot and feasibility study to prepare a comprehensive population-based genetico-epidemiological study on various gene-environment interactions that should be carried out in the very next future. The infrastructure of GGFRC offers us a unique opportunity to build collectives of multiple-thousand people in a shortest period of time and to perform genetic studies as they have not yet been taken in Africa in this form so far. The population is ideally suited to study the impact of polygenic risk profiles of various psychiatric disorders on behavioral traits and their interaction with environment.

Disclosure

Nothing to Disclose.

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T58. AN ENDO-PHENOTYPE APPROACH TO THE GENETICS OF ALCOHOL DEPENDENCE: A GENOME WIDE ASSOCIATION STUDY OF FAST BETA EEG IN FAMILIES OF AFRICAN ANCESTRY

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Background: Fast beta (20-28 Hz) electroencephalogram (EEG) oscillatory activity may be a useful endophenotype for studying the genetics of disorders characterized by neural hyper-excitability, including substance use disorders (SUDs). However, the genetic underpinnings of fast beta EEG have not previously been studied in a population of African-American ancestry (AA), an understudied population in the genetics of addiction.

Methods: In a sample of 2,382 AA individuals from 482 families drawn from the Collaborative Study on the Genetics of Alcoholism (COGA), we performed a Genome-Wide Association Study (GWAS) on resting-state fast beta EEG power. To further characterize our genetic findings, we examined the functional and clinical/behavioral significance of GWAS variants.
Results: Ten correlated SNPs ($r2 > 0.9$) located in an intergenic region on chromosome 3q26 were associated with fast beta EEG power at $p < 5x10\text{-}8$. The most significantly associated SNP, rs11720469 (β: -0.124; $p < 4.5x10\text{-}9$), is also an eQTL for BCHE (butyrylcholinesterase), expressed in thalamus tissue. Four of the genome-wide SNPs were also associated with DSM-IV Alcohol Dependence in COGA AA families, and two (rs13093097, rs7428372) were replicated in an independent AA sample (Gelernter et al., 2014). Analyses in the AA adolescent/young adult (offspring from COGA families) subsample indicated association of rs11720469 with binge drinking.
Discussion: Converging data presented in this study provide support for the role of genetic variants within 3q26 in neural and behavioral disinhibition. These novel genetic findings highlight the importance of including AA populations in genetics research on SUDs, and the utility of the endophenotype approach in enhancing our understanding of mechanisms underlying addiction susceptibility.

Disclosure

Nothing to Disclose.

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T59. INCORPORATING FUNCTIONAL GENOMIC INFORMATION TO CHARACTERIZE POLYGENIC SIGNAL AND IDENTIFY VARIANTS ENRICHED FOR GENE-BY-ENVIRONMENT INTERACTION FOR YOUNG ADULT ALCOHOL PROBLEMS

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Background: Polygenic scoring has emerged as one way to characterize aggregate genetic risk; however, the conventional methods for calculating polygenic scores contain a mixture of "true" genetic signal and random noise. We hypothesized that functional genomic information could be used to enhance polygenic signal to predict young adult alcohol use, and to identify genetic variants (single nucleotide polymorphisms; SNPs) likely to be enriched for gene-by-environment interaction. In polygenic analyses in the FinnTwin12 sample, variants located under a DNase I peak or in linkage disequilibrium with a SNP under a DNase I peak (i.e., in an open chromatin region and likely to have a regulatory function) had per-SNP effects that were > 3.5 times higher than non-DNase SNPs. Furthermore, DNase SNPs were enriched for gene-by-environment interaction compared to SNPs filtered by p-value only ($p = .047$) in tests where romantic relationship status was the environmental moderator. This project examines the use of functional annotation information to improve polygenic risk prediction and the implications for studies of measured gene-environment interaction.

Disclosure

Nothing to Disclose.

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T60. INVESTIGATING THE ROLE OF ONE-CARBON METABOLISM PATHWAY IN COMPLICATED ALCOHOL WITHDRAWAL STATES

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Background: Complicated withdrawal states in alcohol dependence syndrome (ADS) include alcohol withdrawal seizures (AWS) and delirium tremens (DT) and are associated with significant medical and psychiatric morbidity. Existing evidence suggests that in patients with chronic ADS, the associated deficiency of vitamin B12 and folic acid could lead to hyperhomocysteinemia through the inhibition of methionine synthase (MS) and methylene tetrahydrofolate reductase (MTHFR) enzymes of the one-carbon metabolism pathway. Hyperhomocysteinemia has been found to be associated with complicated alcohol withdrawal especially withdrawal seizures (AWS). The common variant of the MS A2756G gene has been found to be associated with lower plasma homocysteine levels. The homozygote variant of the MTHFR A1298C gene results in partial loss of enzyme activity. Thus, it may be worthwhile to study the above SNPs in patients with complicated alcohol withdrawal states and correlate the findings with plasma homocysteine, vitamin B12 and folate levels.
Methods: In our study, we aimed to investigate the association of MTR A2756G (responsible for the MS enzyme) and MTHFR A1298C polymorphisms with complicated withdrawal states i.e. AWS and delirium tremens (DT). We also measured levels of plasma homocysteine, vitamin B12 and folate in these patients. The sample consisted of a total of 150 male patients with ADS of which 84 patients had simple withdrawal state (SWS), 30 patients had DT and 36 patients had AWS. Assessments included a general physical examination, biochemistry panel, a complete blood count, assays of plasma homocysteine, vitamin B12 and folate along with

genotyping for the MTR A2756G and MTHFR A1298C polymorphisms.

Results: There was no difference in the mean age at onset of dependence (SWS - 28.2 ± 5.7; DT - 28.2 ± 4.6; AWS - 27.9 ± 5, F = 0.03, p = 0.9). However, there was a significant association between the mean daily units of alcohol consumed and complicated alcohol withdrawal states. (SWS - 13.6 ± 3.7; DT - 19.8 ± 3.9; AWS - 17.1 ± 4.9, F = 27.8, p <0.05).

The study also found no differences in the serum homocysteine levels (SWS – 0.91; DT – 0.91; AWS – 0.88 nmol/ml, t = 0.9, p = 0.6), vitamin B12 levels (SWS – 274; DT – 265; AWS – 230 pg/ml, t = 1.2, p = 0.5), and folate levels (SWS – 99.3; DT – 99.1; AWS – 98.2 pg/ml, t = 2.4, p = 0.1). Although vitamin B12 and folic acid levels fell in the lower end of the normal range, no deficiency states were observed. No association was found between levels of plasma homocysteine, vitamin B12 & folic acid levels and complicated alcohol withdrawal states.

No significant differences were found between the groups with respect to haematological and biochemical parameters examined. The two groups did not differ significantly with respect to genotype frequency of the SNPs examined (MTHFR A1298C and MTR A2756G).

Discussion: Our study finds that it is the quantity of alcohol consumed in a day that is associated with complicated withdrawal states with frequent heavy drinkers more likely to have severe withdrawal. It would be worthwhile to explore this further as no clear genetic risk factors emerged. The study was limited by its sample size, the use of cross-sectional sampling method and the exclusion of female patients from the study. However, it is one of the first studies to examine these SNPs in a south Indian population. The role of the one-carbon metabolism pathway in these states remains an important area of research with numerous possible treatment implications.

Disclosure

Nothing to Disclose.

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T61. INTEGRATION OF GENE EXPRESSION WITH GWAS TO IDENTIFY RISK GENES FOR NICOTINE DEPENDENCE

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Background: Cigarette smoking is addictive and persistent smoking leads to nicotine dependence. Both family and twin studies have indicated that it is influenced by genetic factors. In recent years, several risk genes for nicotine dependence have been identified. However, these genes account for only a small proportion of observed heritability. It is a challenge to discover those remaining genetic factors. FTND score is a common measure for nicotine dependence, and the time to smoke the first cigarette in the morning (TFC) can be considered as a measure of nicotine withdrawal since the half-life of nicotine in human blood is about 2 hours.

Methods: To identify genes involved in these phenotypes, we performed a gene-based genome-wide meta-analysis of FTND score and TFC using several African American samples from dbGaP. We also conducted transcriptome sequencing for samples isolated from nucleus accumbens of chronic nicotine treated and withdrawal mice.

Results: By integrating differentially expressed genes in nicotine treated and withdrawal mice with GWAS meta-analyses, we discover some novel genes associated with nicotine dependence and withdrawal. These include TEAD3, ORC3, TCTN3, and SERPINE2. These genes are reported associated with schizophrenia, neuronal maturation, orofaciodigital syndromes and cancers.

Discussion: Our results indicate that integration of functional data with GWAS analyses could significantly improve power to discover new risk genes.

Disclosure

Nothing to Disclose.

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T62. LONGITUDINAL CHANGES IN GLUCOCORTICOID RECEPTOR 1F METHYLATION AND PSYCHOPATHOLOGY AFTER MILITARY DEPLOYMENT

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Background: The glucocorticoid receptor (GR) 1F region is involved in transcription and expression of the GR protein and influences hypothalamic-pituitary-adrenal (HPA)-axis activity. Several studies have investigated GR-1F DNA methylation in the context of traumatic stress and psychiatric disorders, such as major depressive disorder and

posttraumatic stress disorder (PTSD). However, longitudinal studies examining GR-1F DNA methylation before and after exposure to traumatic stress are lacking. We therefore aimed to investigate prospective DNA methylation changes in the GR-1F region after military deployment and its relation to the emergence of psychopathology.
Methods: Whole blood DNA methylation in the entire GR-1F region (52 CpGs) before and six months after deployment was quantified using pyrosequencing (N=92). Methylation levels were linked to post-deployment mental health problems (Revised Symptom Checklist, SCL-90), PTSD symptoms (Self-Rating Inventory for PTSD) and trauma exposure during deployment. Moreover, methylation was related to GR-1F expression, GR binding and genetic variation in the GR. Mean methylation, the number of methylated sites (methylation burden), mean methylation at transcription factor binding sites and at CpGs significantly associated with GR-1F expression (functional methylation) were examined.
Results: Trauma exposure during deployment and the emergence of mental health problems were significantly related to an increased methylation burden (t=2.23, p=2.8x10-2, =0.45 and t=2.24, p=2.7x10-2 and =0.085, respectively), which was associated with both decreased GR-1F expression (t=-2.92, p=4.7x10-3, =-1.93) and GR binding (t=-2.13, p=3.9x10-2, =-2.9x10-3). Moreover, development of psychopathology symptoms was significantly associated with increased methylation at functionally relevant CpGs (mental health problems: t=3.73, p=3.5x10-4, =1.2x10-2; PTSD symptoms: t=2.10, p=3.8x10-2, =0.59). Change in mean methylation was associated with a change in mental health problems (t=1.99, p=5.0x10-2, =4.1x10-3) and in GR-1F expression (t=-2.35, p=2.2x10-2, =-0.074).
Discussion: This longitudinal study in a military cohort shows that GR-1F DNA methylation levels are related to trauma exposure during deployment and the development of post-deployment psychopathology symptoms, particularly at functionally relevant sites. Together, our results provide further insight in transcriptional regulation of the glucocorticoid receptor gene, by demonstrating that GR-1F DNA methylation levels can vary over time and are related to stress vulnerability and the emergence of post-deployment psychopathology symptoms.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.550

T63. THE INTERGENERATIONAL EFFECTS OF TRAUMA: INTEGRATING NARRATIVE AND NEUROSCIENCE TO UNDERSTAND ADVERSITY AND RESILIENCE

Hannah Kliger

The Pennsylvania State University

Background: The evidence for vulnerability and resilience as responses to traumatic events points to a range of long-term effects following trauma. The factors that modify the adaptation to trauma include the environment and prior experience. This study compares recent work in the field of neuroscience, particularly the application of epigenetic methods to trauma studies, with findings related to the transformative power of trauma narratives.
Methods: The Transcending Trauma Project has collected and analyzed 300 in-depth narratives of Holocaust survivors and their family members. Our approach points to the influence of narratives shared about the memories of trauma on shaping the worldview of those who listen. The Transcending Trauma Project team has focused on the comprehensive study of coping and adaptation after extreme trauma through the expansion of current paradigms by applying the principles of qualitative research to the study of a large sample consisting of family units comprised of intergenerational members of the same family. The challenge we faced included devising methods for the management of a large data set and methods for assessing qualitative narrative material on the individual and family system levels. Our observations are compatible with recent epigenetic modifications that have been shown to correlate with the intergenerational transmission of posttraumatic stress disorder risk.
Results: When a particular attribute of a survivor parent is emotionally compelling, this attribute can become an organizing value system in the identity of the child. We have framed the process as the communication of transformative narratives. Integrating epigenetics into a model that probes the mechanisms through which the meaning of prior experience is expressed and transmitted is consistent with the approach we have used to trace the impact of pivotal narratives.
Discussion: Through this analysis, we underline the importance of a developmental view that evaluates the complex biological and psychological processes that contain both the elements of positive adaptation and negative consequences as they are experienced by trauma survivors and their offspring

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.551

T64. GENOME-WIDE ASSOCIATION STUDY OF POSTTRAUMATIC STRESS DISORDER SYMPTOMS IN TWO COHORTS OF UNITED STATES ARMY SOLDIERS

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Background: Posttraumatic stress disorder (PTSD) is a prevalent public health concern and genetic study of PTSD can provide insight into the etiology of the disorder. Several genome-wide association studies (GWAS) on PTSD have been published, including our GWAS on PTSD in the Army Study of Risk and Resilience in Servicemembers (Army STARRS). Each GWAS reported findings on genetic loci associated with PTSD risk. However, to better understand the potential mechanisms involved in PTSD development, we proposed to identify genetic loci associated with specific PTSD symptoms. To achieve the goal, we conducted a GWAS on the severity of three PTSD symptom domains in two US Army cohorts.
Methods: We performed genome-wide analysis in two cohorts in the US Army: the New Soldier Study (NSS) and the Pre/Post-Deployment Study (PPDS). A total of 8,920 European American, 1,932 African American, and 2,622 Latino American samples with traumatic experiences were included in the analysis. Genotype data were processed for quality control, and imputed to the 1,000 Genomes Project reference panel using SHAPEIT and IMPUTE2 software. The life-time severity of three PTSD symptom domains (re-experience, avoidance, and hyper-arousal) were analyzed. The PTSD symptoms were collected by an abbreviated version of PTSD Checklist with 6 questions. The primary association analyses were performed within each ancestral group and cohort using linear regression model adjusted for 10 within-ancestral group of principal components, age, and gender. Results were then meta-analyzed within ancestral groups across cohorts. SNP-based heritability was estimated using LD score regression in European American samples.
Results: In the meta-analysis between NSS and PPDS, we identified 1 locus for severity of re-experiencing in the European American samples (chr. 5, rs2311207, beta = 0.26, p-value = 2.88x10$\hat{}$-9) and 1 locus for severity of hyper-arousal in Latino American samples (chr10_6953246_D, beta = 1.64, p-value = 3.85x10$\hat{}$-10) with genome-wide significant association (at significant level 5x10$\hat{}$-8 / 3 = 1.67x10$\hat{}$-8). External replication is needed to further confirm these associations. All genome-wide analyses show no sign of confounding (lambda_GC from 0.992 to 1.010). We did not found significant SNP-based heritability for the severity of the three PTSD symptoms domains.
Discussion: In a large GWAS of PTSD symptoms based on US Army sample, we found 2 loci associated with severity of PTSD symptom domains, including re-experiencing and hyper-arousal. Replication of these results in independent samples are needed. As in previous GWAS on PTSD, larger sample size is needed to further characterize the SNP-based heritability and genetic correlation between PTSD symptoms and other psychiatric disorders.

Disclosure

Nothing to Disclose.

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T65. THE INFLUENCE OF THE GLUTAMATERGIC SYSTEM ON COGNITION IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW

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Background: Patients with schizophrenia have been estimated to be one to two standard deviations below the scores of healthy controls in terms of cognitive function. Cognitive performance is also impaired in unaffected biological relatives compared to the general population, indicating a genetic contribution to the cognitive impairment. It has been suggested that the glutamatergic system influences cognition and several investigations have explored the relationship between glutamate and cognitive deficits in schizophrenia. However, previous literature indicating a

role of the glutamatergic system in cognitive deficits in schizophrenia has been inconclusive. The aim of this study was to systematically review candidate gene studies influencing the glutamatergic pathway and explore the impact on cognition in schizophrenia.

Methods: 11 relevant candidate gene studies were identified through systematic search following PRISMA guidelines and were reviewed. Ovid MEDLINE, PsychINFO and EMBASE were searched using the following truncation keyword search terms 'schizophrenia', 'glutamat', 'cognit', 'adult', 'human', 'patient' and 'control.' To be included, studies must have observed at least one objective measure of cognitive performance in patients with schizophrenia and had to be candidate gene studies focused on the glutamatergic pathway. Animal studies and studies that did not have a schizophrenia or schizoaffective patient study group were excluded.

Results: Results were examined according to cognitive domain. Of the cognitive domains observed, memory and working memory were most consistently influenced by genetic variation along the glutamatergic pathway. DTNBP1 were associated with verbal and visual memory and working memory performance (n = 565). GRM3 was significantly associated with episodic memory (n = 508). DTNBP1 is involved in the storage and release of GRM3, which encodes mGlu3 (shown to modulate glutamate neurotransmission and synaptic plasticity). G72 activates DAAO, which is involved in the metabolism of D-serine and was significantly associated with episodic memory and working memory (n = 292). NRG1, ErbB4 and AKT1 genes were significantly associated with working memory only (n = 661). NRG1 has a biological role in brain development and neural function which has been shown to be partially mediated by the NMDA-glutamate pathway, with ErbB4 and AKT1 directly linked to NRG1 downstream.

Discussion: Findings from this systematic review suggest that the glutamatergic system contributes to the cognitive deficits in schizophrenia, in particular in the areas of memory and working memory. Literature suggests that DTNBP1 and GRM3 are involved in the presynaptic components synthesis and uptake in the glutamatergic pathway, while NRG1 and its downstream signalling are involved in post-synaptic scaffold and signalling. As the difference between memory and working memory appears to be NRG1 and its downstream effects, results indicate presynaptic components synthesis and uptake of glutamate is involved in memory, while post-synaptic scaffold and signalling appears to be involved in working memory. Different parts of the glutamatergic pathway appear to be associated with different cognitive domains, highlighting the importance for cognition to be examined by domain as opposed to globally. By breaking down cognition into multiple domains, it will be easier to identify the molecular mechanisms affecting different cognitive phenotypes in schizophrenia.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.553

T66. THE NEUREGULIN-1 GENE IS ASSOCIATED WITH SCHIZOTYPY IN THE GENERAL POPULATION

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Background: It is believed that the personality characteristics and symptoms observed in schizophrenia lie on a continuum, with subclinical symptoms referred to as schizotypy. The continuum theory of schizophrenia recognises schizotypy as a suitable model for investigating schizophrenia: individuals with high levels of schizotypy demonstrate similar symptoms, cognitive profiles and neuroimaging findings to schizophrenia, albeit in a more subtle manner, without the potential confounding factors associated with schizophrenia. Both schizophrenia and schizotypy have been shown to be influenced by genetic factors. Neuregulin-1 (NRG1), involved in neuronal development, migration, myelination and synaptic plasticity, has been identified as a promising candidate gene for schizophrenia risk. Several NRG1 single nucleotide polymorphisms (SNPs) have been associated with schizophrenia and cognitive deficits, though only one SNP has been previously associated with schizotypy. The aim of this study was to examine the link between

NRG1 and schizotypy across the schizotypy/schizophrenia continuum.

Methods: Participants were 200 adults (83 patients with schizophrenia and 117 healthy controls) who were assessed for schizotypy factors using the Oxford-Liverpool Inventory of Feelings and Experience (O-LIFE). The factors assessed were unusual experiences (UnEx), introvertive anhedonia (InAn) and cognitive disorganisation (CogDis), which are thought to reflect the positive, negative and cognitive symptoms of schizophrenia respectively. Participants were also genotyped for five NRG1 SNPs; rs10503929, rs3924999, rs2466058, rs35753505 and rs6994992. A MANOVA was conducted with schizotypy factors as dependent variables and participant group as independent variables to observe differences between patients and controls. Another MANOVA was conducted with schizotypy factors as dependent variables and NRG1 SNPs as independent variables to observe differences and interactions of the NRG1 SNPs on schizotypy across the continuum.

Results: Confirming previous findings, schizotypy scores were significantly higher in the patient group as compared to controls ($p < 0.001$). There were no significant differences in schizotypy scores for individual SNPs. However, significant interactions were observed between rs10503929 and rs3924999 ($p = 0.006$) and between rs10503929 and rs2466058 ($p = 0.007$) for combined schizotypy variables. Non-significant interaction trends were observed between rs10503929, rs3924999 and rs2466058 ($p = 0.034$) and between rs6994992, rs10503929 and rs2466058 ($p = 0.11$). Post-hoc analysis showed significant interaction between rs10503929 and rs3924999 for UnEx ($p = 0.008$) and non-significant interaction trends between rs10503929 and rs3924999 ($p = 0.012$) and rs10503929 and rs2466058 ($p = 0.018$) for CogDis.

Discussion: This is the first study to demonstrate an association between NRG1 and schizotypy across the continuum, in particular CogDis. From this, it can be inferred that genetic variation in NRG1 may be a contributing factor to cognitive deficits in the clinical population, consistent with previous findings. As individual SNPs were not significantly associated with schizotypy but significant interactions were observed, this study also demonstrates the heterogeneity of schizophrenia. This finding contributes to the literature associating NRG1 with cognitive deficits in schizophrenia and supports the use of schizotypy as a model for schizophrenia.

Disclosure

Nothing to Disclose.

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Tuesday, November 1, 2016
13:15 - 15:15
Concurrent Symposia Session 6:

ETHICAL CHALLENGES IN PSYCHIATRIC GENOMIC MEDICINE

Paul Appelbaum (Chair)[1], Maya Sabatello (Co-chair)[2], Jordan Smoller (Discussant)[3]

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Overall Abstract

As genomic technologies are used increasingly in psychiatric research, and make inroads into clinical care for certain psychiatric disorders (e.g., autism), psychiatrists are pondering the ethical issues that will arise with greater availability of genomic data. This symposium considers the spectrum of issues, ranging from consent for genome sequencing (GS) to minors' roles in deciding on genomic testing, to discriminatory requirements that may inhibit psychiatric genetic research, to privacy concerns raised by mobile technologies for transmitting genomic data. Concerns about these issues are heightened by the cognitive and emotional impairments, and by the societal stigmatization, of many psychiatric disorders.

Based on surveys of genomic researchers, Dr. Appelbaum will consider consent for GS. A majority of researchers endorse disclosure of a large amount of information, but are willing to devote limited time to the process. That suggests a need for innovative consent models, but despite their liabilities, traditional approaches to consent are currently seen as most viable. However, there is considerable interest in developing staged consent. This presentation will review challenges to obtaining consent for GS; data on researchers', clinicians', and patients' preferences for information; and potential approaches to meaningful choices for participants and patients about GS and return of results.

Dr. Sabatello will consider adolescents' roles in decisions about GS. Minors may be a particular target of genomic testing for psychiatric disorders, because many psychiatric conditions begin before adulthood and parents want to know their children's genetic make-up. How should we balance parents' informational interests and minors' right (not) to know? What should the response be to genetic results indicating predispositions to psychiatric conditions? Who should decide? These issues are complicated by adolescents' individuation from their families, along with impulsivity, risk-taking, and susceptibility to peer pressure. This presentation will review existing studies, consider

ethical and social challenges, and identify areas for future research.

Dr. Mascalzoni will review discrimination against psychiatric patients in biobank-based, genomic research. A desire to protect vulnerable subjects often leads to restrictions on recruitment of psychiatric patients or expensive screening and follow-up procedures. As a result, biobanks may fail to contain samples from persons suffering from psychiatric disorders. From a desire to protect the vulnerable, we risk creating a situation where they are twice discriminated against: non-inclusion to protect them from the risks of research leads to biased results, which could lead to a lower standard of care in the future.

Finally, Dr. Greenbaum will address privacy issues related to mobile medical applications (MMAs) for genomic information. MMAs offer diagnoses of psychiatric disorders based on phenotypic information and family histories, and are used for deciphering genomic information as well, through increasingly popular DNA apps. In addition to concerns about unfiltered diagnoses and risk estimates of mental disorders, without effective oversight MMAs lack the trustworthiness of other medical devices, and often fail to encrypt data they collect and share with third parties. One approach to this problem is a type of middleware that would prevent MMA genomic data from being shared irresponsibly online.

Disclosure

COVR, Inc. - Equity interest, Self

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PSYCHIATRIC GENOMIC DILEMMAS IN ADOLESCENCE

Maya Sabatello

Columbia University

Abstract

Advances in genetics, data analysis technologies, and the practice of precision medicine are slowly entering the field of psychiatry and raise hopes for better diagnosis, prevention, and treatment of psychiatric disorders. As genetic testing for predispositions to and diagnosis of psychiatric disorders is developed, children may be a particular target group. Studies indicate that parents desire to learn all about their children's genetic make-up–primarily out of a sense of responsibility to care for their children but also due to curiosity–and that testing laboratories and pharmaceutical companies are already invested in marketing their products in this area. Use of genetic tests in children may be motivated further by the fact that many psychiatric conditions begin in childhood and adolescence, although the social, healthcare, and income costs associated with psychiatric disorders endure well beyond childhood.

However, the prospect of psychiatric genetic testing of children, especially asymptomatic children in research settings, and return of secondary genomic findings to them and their families raise unique dilemmas. How should we balance parents' informational interests and children's right (not) to know? What should the response be to genetic results indicating predispositions to psychiatric conditions (e.g., schizophrenia, substance use disorders)? Should the answers to these questions turn on the availability of effective preventive measures? And who should decide?

These challenges are exacerbated for adolescents (ages >13), who are legal minors but whose decision making capacity can often resemble that of adults. The unique characteristics of adolescence further pull the discussion in two conflicting directions. On the one hand, adolescents are engaged in a search for individual identity, in planning for the future, and in individuating from their families, which suggest the value of granting them greater control over decisions regarding genetic testing. On the other hand, adolescents often manifest greater impulsivity and tendencies to engage in risky behaviors and to be influenced by peer pressure, which suggest that their decision-making capacity may be compromised. This may have particular implications for psychiatry: studies suggest that the majority of teens with substance abuse issues began using drugs or alcohol as a result of peer pressure, and that the use of such substances increases the risk for other psychiatric conditions (e.g., schizophrenia). Whether adolescents would resist such pressures in light of psychiatric genetic testing results is unknown, but important to explore.

This presentation will review existing studies relating to the psychiatric genetic testing of adolescents and consider the ethical and social challenges that arise, in particular: adolescents' preferred decision-making roles; types of primary and secondary genomic findings to be returned; impact of psychiatric genetic knowledge on the adoption of prevention measures; and genomic privacy among family members. In addition, suggestions for future research will be considered.

Disclosure

Nothing to Disclose.

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REVERSE DISCRIMINATION FOR PSYCHIATRIC GENETIC STUDIES IN POPULATION-BASED BIOBANKS

Deborah Mascalzoni

Uppsala University Centre or Research Ethics and Bioethics, Sweden

Abstract

The results of genome-based research are increasingly becoming part of planning for care. The question remains

whether the results of this research are representative, since it often excludes people with psychiatric conditions. Despite best intentions, in our desire to protect the vulnerable, we risk creating a situation where they are discriminated against in a double sense: non-inclusion to protect them from the risks of research leads to biased results, that in turn could lead to a lower standard of care in the future.

Large-scale population biobanking projects link genetic data with the information participants provide regarding their health status, lifestyle (including alcohol consumption, smoking, etc.) and known environmental factors. The collection of samples and data constitutes the basis for future research projects on two levels. First, some diseases or phenotypes are collected with great precision during the recruitment for existing research protocols. Second, follow up projects are planned based on the analysis of data collected from questionnaires and analysis of biological specimens on the basis of identified phenotypes. Often, these data make it possible to assess and identify diseases ranging from diabetes to depression. Once a condition is identified, researchers need to collect further phenotypes or dig deeper into a recognized pattern.

Commonly, participants in population cohorts are recruited for studies of common diseases. For example, there is a large number of cohorts focused on cardiovascular and metabolic conditions. Recruitment of population cohorts often excludes incapacitated individuals and people who, for several reasons, cannot provide a full informed consent. This means minors are often excluded from population cohorts and (sometimes) instead collected separately in biobanks for children. Against this background, it becomes obvious that there is a problem of representativeness for these categories of people that constitute an already known first bias in the collections. The reason for this is often administrative: handling issues of legal representatives may in fact prove to be too complicated on a population level.

There is, however, a second layer of possible bias that arises in the planning of follow up research projects. Planning to recall people with severe depression, addiction or initial stages of degenerative conditions (dementia, etc.), often entails several layers of ethical and logistical issues that do not arise in re-contact of participants with suspected diabetes or leukemia.

If we use depression as an example, this problem becomes apparent. When people suspected to have depression are invited to participate in follow up research with a physician, they are asked to fill out questionnaires used to diagnose depression and identify suicide risks. Costly follow up visits with specialists are needed if a research participant discloses that he or she is contemplating suicide. For people with early stage dementia, the problem is more related to information and ability to pay attention, and the difficulties associated with explaining and understanding large amounts of complex information.

This presentation will provide an overview of possible discriminatory patterns that jeopardize the possibility for psychiatric patients (in a very broad sense) to benefit from the potential of biobank-based research, with some case examples.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.557

LEGAL AND ETHICAL IMPLICATIONS IN GENOMICS AND MENTAL HEALTH

Dov Greenbaum

Interdisciplinary Center Herzliya, Israel

Abstract

In a 2014 guidance document the US FDA stressed its intent to regulate mobile medical applications, (MMAs), including the smartphone 'apps' that help patients with diagnosed psychiatric conditions, including, for example, PTSD, depression, anxiety and OCD, "maintain their behavioral coping skills." However, recent enforcement efforts by another federal authority, the FTC have signaled the FDA's intent to now avoid regulating MMAs.

The regulation of MMAs, or the lack thereof, is of great interest to the mental health community. Not only can MMAs ostensibly test and diagnose psychiatric disorders based on phenotypical information and family histories, but there is a growing use of MMAs for deciphering genomic information as well, through increasingly popular DNA app stores. These apps are not just recreational in nature, but have the potential to provide users with diagnostic-like information without the help of a health care provider intermediary.

However, the use of these apps can quickly become problematic. Just like in areas of physical health we have seen an increase in both the walking sick —i.e., those individuals that have received relevant health related information and have chosen to ignore it— and the worried well —i.e., those individuals who have received uninformative health related genomics information but have chosen an illogical reaction— we will likely see similar phenomenon in the area of mental health.

In addition, unlike their medical device counterparts, without real and effective oversight, MMAs lack not only the trustworthiness of other components within the medical system, they also often lack encryption of data that they collect and share with third parties. This is particularly problematic given inherent societal stigmas associated with mental health. Along these lines, genomic apps are especially problematic as seemingly benign genetic correlations today can become socially problematic genetic correlations in the future. Genomic apps that promote the sharing of even seemingly recreational-minded genetic correlations could create particularly problematic somewhat immutable internet records of potentially problematic data in the future.

To this end, we propose a type of middleware that would serve to prevent data from being shared irresponsibly online. As a sanctioned clearinghouse for MMA created data and results, this middleware would be a portal for potentially relevant medical and genomic data originating in MMAs on smartphones and the like, and that end up at third parties. In lieu of top-down government regulations, this conduit would self-regulate the industry by providing minimal levels of consistent encryption of medical data. Originating data that did not rise to these levels of encryption would not be pasted on to the reputable third parties such as medical professionals and hospitals. Further, with the FDA out of the MMA regulation business, it is imperative that

MMAs strive toward minimum standards of efficacy and usefulness. Again, reputable third parties would not accept data unless it passed through the middleware, and the middleware would not accept data unless it the originating MMAs met minimal requirements as set by industry groups. While this middleware is far from a perfect solution for concerns relating to privacy and security, particularly as it relates to genomic data at rest and in transit and associated with smartphones, it is a feasible start.

Disclosure

Nothing to Disclose.

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MODELS OF INFORMED CONSENT FOR GENOMIC SEQUENCING

Paul Appelbaum

Columbia University

Abstract

Genome sequencing (GS) is becoming prevalent in medical research and making its way into clinical practice. Although genetic testing is used less frequently in psychiatry than in some related medical specialties, such as neurology, its use is growing, e.g., for the diagnosis of neurodevelopmental syndromes with psychiatric components, such as DiGeorge's syndrome and Fragile X. Psychiatric researchers are using GS to explore the genetic etiology of disorders such as schizophrenia, bipolar disorder, autism, and intellectual disabilities and its clinical use seems likely to follow. Hence, psychiatric researchers and clinicians need to grapple with how best to obtain informed consent for GS.

A number of challenges exist for the consent process, including the large amount of information that needs to be conveyed. Persons facing choices about GS must understand, along with the standard disclosures that accompany any clinical or research consent: the nature of their situation and why the test is being recommended; likely benefits and risks, such as discrimination in insurance; and how secondary findings will be dealt with—a particularly difficult topic because at the time researchers and clinicians will know neither the likely findings nor their potential implications. Moreover, persons affected by psychiatric disorders may have difficulties in attention and information processing that can complicate their assimilation of this information.

To explore approaches to consent for GS, we surveyed 254 genetic researchers in the US, almost all of whom had used or anticipated using GS. A majority endorsed discussion of a wide range of risks (e.g., negative psychological responses) and benefits (e.g., early detection of disorders, enhanced life-planning), along with information about possible impact of findings on family members; protections for confidentiality; procedures related to return of data should participants become impaired or deceased; whether findings from subsequent research or advances in interpretation would be offered; and whether and how choices about return of findings could be overridden. When return of secondary findings is possible, these discussions will have to cover both primary and secondary results, and explanations of a number of choices about receipt of results and use of samples.

However, it is clear that neither clinicians nor researchers have time for such extended discussions, especially given the limits of popular knowledge of genetics. Thus, innovative models of informed consent will need to be developed. Based on our survey findings, we identified 4 such models: traditional consent, staged consent, mandatory return, and outsourced consent. A follow-up survey of 198 genetic researchers found that, despite their liabilities, traditional approaches to consent are seen as the most viable under current circumstances. However, there is considerable interest in staged consent, assuming the infrastructure to support it can be provided.

This presentation will review the challenges to obtaining informed consent for GS; data on researchers', clinicians', and patients' preferences for information; and potential approaches to consent that will allow participants and patients to make meaningful choices about genomic sequencing and return of results.

Disclosure

COVR, Inc. - Equity interest, Self

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Concurrent Symposia Session 7:

THE OTHER GENOME: PATHWAYS FOR THE EFFECTS OF THE MICROBIOME ON METABOLISM, BEHAVIOR, AND MENTAL DISORDERS

Julio Licinio (Chair)[1], Ma-Li Wong (Co-chair)[2], Bernard Lerer (Discussant)[3]

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Overall Abstract

Major efforts are ongoing to unravel the genomic basis of psychiatric disorders, with a focus on the human genome. The amount of microbial cells exceeds that of human cells in our bodies. The immense amount of non-human DNA within our bodies is not captured by traditional human genomic studies. Our microbial component is represented by approximately 1,000 different species. This symposium will address the behavioral effects of our "other genome": the human microbiome. The microbiota-gut-brain (MGB) axis is a complex

multiorgan bidirectional signaling system between the microbiota and the brain that plays a fundamental role in host physiology, homeostasis, development, metabolism and behavior. Growing evidence shows reproducible and consistent effects of microbial states on behavior, supporting a role for the microbiota in modulating behavior. Differences in anxiety-related behaviors are commonly reported in mice with altered gut microbiomes, implicating the role of gut microbiota in stress and depression. In this symposium, Dr. Omry Koren, Bar-Ilan University, Israel, will present data on how microbes can influence mood and behavior. Dr. Peng Xie, Chongqing Medical University, China, will present exciting new data showing that the absence of gut microbiota in germ-free mice results in decreased depressive-like behavior. His team shows that from clinical sampling, the gut microbiotic compositions of healthy controls are significantly different from those of depressed patients. Finally, fecal microbiota transplantation of germ-free mice with 'depression microbiota' from depressed patients results in depression-like behaviors compared with colonization with 'healthy microbiota' from healthy individuals. Moreover, they showed that mice harboring 'depression microbiota' primarily exhibited disturbances of microbial genes and host metabolites involved in carbohydrate and amino acid metabolism, indicating that the development of depressive-like behaviors is mediated through the host's metabolism. Dr. Julio Licinio, South Australian Health & Medical Research Institute (SAHMRI) and Flinders University, Australia, will show data on how a model of chronic stress, resulting in depressive-like behaviors, causes change in gut microbiota composition. Dr. Ma-Li Wong, SAHMRI and Flinders, Australia, will present data demonstrating that that the inflammasome, as evidenced by genetic or pharmacologic inhibition of caspase 1, mediates behavioral changes that might be brought about through the MGB axis. In this symposium we will demonstrate that MGB axis is fully bidirectional, functioning in a manner through which variation in microbiota affect behavior, while alterations in behavior, brought about by chronic stress, genetic manipulation or pharmacological intervention, result in changes in the gut microbiota. Further elucidation of the MGB axis may offer novel therapeutic targets for psychiatric disorders.

Disclosure

Nature Publishing Group - Editor, receiving honoraria, Self

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MOODY MICROBES: DO MICROBES INFLUENCE OUR BEHAVIOR?

Omry Koren

Bar Ilan University

Abstract

A growing body of literature indicates that our "second genome"- the genes in our resident microorganisms (microbiome) - affects many aspects of our physiology. From this perspective, we are "supraorganisms" coated and inhabited by a number of microbial cells that are 10 times greater than the sum of all our human somatic and germ cells, carrying150 fold more genetic information than our own human genome. The intestine contains the largest collection of microbes among all of our body "habitats" (sites for microbial colonization). Together, gut microbes form a community, or microbiota, that has a major impact on health through interactions with host cells (including components of the innate and adaptive immune systems), extraction of nutrients and energy from the diet, and complex biotransformations of a variety of ingested compounds, including potential carcinogens. Shifts in microbiome composition occur at different stages in life, from infancy, through puberty and gestation, to old age. Changes in the composition of the gut microbiome (dysbiosis) have also been associated with different disease states such as obesity, inflammatory bowel disease (IBD), diabetes, and metabolic syndrome.

It is also becoming widely known that our gut microbiome has important effects on our moods and behavior. Studies have linked gut bacterial composition with risk taking, anxiety, stress, mating and sexual preferences in animals. These are concurrent with alterations found in serotonin levels, levels of brain derived neurotrophic factor (BDNF), and exaggerated corticosterone release in response to stress. Germ free animals also provide an important tool to study the contribution of the microbiota as they have altered serotonergic function in the central nervous system and different behavioral patterns. Taken together, the data indicates the important roles of microbiota in host behavior.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.561

ALTERATING THE GUT MICROBIOME BY MICROBIOTA TRANSPLANTATION FROM DEPRESSED PATIENTS INTO GERM-FREE MICE RESULTS IN DEPRESSIVE-LIKE BEHAVIORS THROUGH A PATHWAY MEDIATED BY THE HOST'S METABOLISM

Peng Xie

Chongqing Medical University, Chongqing, China

Abstract

Major depressive disorder (MDD) is the result of complex gene–environment interactions. MDD is a leading cause of disability worldwide, and it is a major contributor to the overall global burden of disease. However, the definitive environmental mechanisms underlying the pathophysiology of MDD remain elusive. The gut microbiome is an increasingly recognized environmental factor that can shape the brain through the microbiota-gut-brain axis. We will present recent data from our lab showing that the absence of gut

microbiota in germ-free (GF) mice resulted in decreased immobility time in the forced swimming test relative to conventionally raised healthy control mice. Moreover, from clinical sampling, the gut microbiotic compositions of MDD patients and healthy controls were significantly different with MDD patients characterized by significant changes in the relative abundance of Firmicutes, Actinobacteria and Bacteroidetes. Fecal microbiota transplantation of GF mice with 'depression microbiota' derived from our MDD patients resulted in depression-like behaviors compared with colonization with 'healthy microbiota' derived from healthy control individuals. Finally, we showed that mice harboring 'depression microbiota' primarily exhibited disturbances of microbial genes and host metabolites involved in carbohydrate and amino acid metabolism. Our data reveal that dysbiosis of the gut microbiome may have a causal role in the development of depressive-like behaviors, in a pathway that is mediated through the host's metabolism. We have demonstrated in these experiments that gut microbiota can physiologically induce depression-like behavior in mice. Moreover, we document characteristic alterations in the gut microbiotic community of MDD patients and show with state-of-the-art techniques that gut microbiota can contribute to depression-like behavior through altering host metabolism. These findings provide an original perspective to uncover the pathologic mechanism(s) underlying depression as well as revealing the need for innovative gut-mediated therapies for depression.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.562

INFLAMMASOME SIGNALLING AFFECTS ANXIETY AND DEPRESSIVE-LIKE BEHAVIORS

Julio Licinio

South Australian Health and Medical Research Institute

Abstract

The inflammasome dysregulation may be implicated in major depressive disorder (MDD). Inflammasome activation causes the maturation of caspase-1 (Casp1, interleukin converting enzyme), which plays a role in a number of physio/pathological processes both in the CNS and periphery (i.e. immune response, microglia activation, LTP, synaptic plasticity, adipocyte differentiation, chronic inflammation). Casp1 causes the activation of interleukin (IL)-1β and IL-18, two pro-inflammatory cytokines involved in neuroimmunomodulation, neuroinflammation, and neurodegeneration. C57BL/6 mice with genetic deficiency were screened for anxiety- and depressive-like behaviors, and locomotion at baseline and after chronic restraint stress (4-6 h/day for 3 weeks). Genetic deficiency of caspase-1 decreased depressive- and anxiety-like behaviors, and increased locomotor activity and skills. Caspase-1 deficiency also prevented the exacerbation of depressive-like behaviors following chronic stress. We suggest that the pathway that links chronic stress to depressive-like behaviors involves the inflammasome. Further work should address whether strategies to block caspase 1 bioactivity may have potential as a novel type of antidepressant treatment.

Disclosure

Nature Publishing Group - Editor, receiving honoraria, Self

http://dx.doi.org/10.1016/j.euroneuro.2016.09.563

INFLAMMASOME SIGNALLING MODULATE THE EFFECTS OF THE MICROBIOME ON BEHAVIOR

Ma-Li Wong

South Australian Health and Medical Research Institute

Abstract

The microbiota-gut-brain (MGB) axis is a complex multi-organ bidirectional signaling system between the microbiota and the brain that plays a fundamental role in host physiology, homeostasis, development and metabolism. We tested whether antagonism of caspase-1 (casp1) would result in gut microbiome changes. Pharmacological antagonism of inflammasome signaling using the casp1 antagonist minocycline ameliorated stress-induced depressive-like behavior in wild-type mice. Either chronic stress or pharmacological inhibition of casp1 altered the fecal microbiome in a very similar manner. Gut microbiota changes in stressed mice treated with minocycline included increased relative abundance of Akkermansia spp and Blautia spp, which are compatible with beneficial effects of attenuated inflammation and rebalance of gut microbiota respectively, and increment in Lachnospiracea abundance which was consistent with microbiota changes of casp1 deficiency. The protective effect of casp1 inhibition may involve modulation of the relationship between stress and gut microbiota composition, through which the gut microbiota via inflammasome signaling modulates pathways that will alter brain function, and affect depressive- and anxiety-like behaviors.

Disclosure

Nature Publishing Group - Editorial Honoraria, Spouse

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Concurrent Symposia Session 8:

A MULTIMODAL APPROACH FOR STUDYING PATHWAYS LEADING TO PSYCHOSIS IN 22Q11 DELETION SYNDROME

Doron Gothelf (Chair)[1], Amos Frisch (Co-chair)[2], Abraham Weizman (Discussant)[3]

[1]*Sheba Medical Center*
[2]*FMCR, Israel*
[3]*Tel Aviv University, Israel*

Overall Abstract

22q11 deletion syndrome (22q11DS), also known as velo-cardio-facial syndrome has been the focus of intensive research over the last 15 years. The syndrome is the most commonly known microdeletion syndrome, occurring in at least 1 to 4,000 live births, and is the most commonly known genetic syndrome associated with schizophrenia, with approximately one-thirds of individuals developing schizophrenia by young adulthood. Thus, 22q11DS provides a homogeneous model from which to learn about the effects of decreased dosage of genes on the development of brain structure and function and consequently on the emergence of schizophrenia-like psychotic disorder.

The proposed symposium consists of leading 22q11DS international researchers and clinicians and young Israeli scientists. The presenters study longitudinally large cohorts of children, adolescents and young adults with 22q11.2DS.

Dr. Gothelf will provide an introduction on the genetic and medical characteristics of 22q11DS. He will also present data on the genotype-neuropsychiatric phenotype associations in 22q11DS and preliminary findings of elevated levels of neuroinflammatory factors in psychotic 22q11DS individuals.

Dr. Gur will describe the common psychiatric comorbidities occurring in two-thirds of individuals with 22q11DS including ADHD, anxiety disorders and psychotic disorders. She will also present longitudinal data following the developmental trajectories of attenuated psychotic symptoms in 22q11DS.

Dr. Kates will summarize a twelve-year longitudinal study of neuroanatomic, neurofunctional and neuropsychological development in youth with 22q11.2 deletion syndrome (22q11DS). Dr. Kates identified aberrant longitudinal alterations in cortical thickness / connectivity, as well as neurocognitive deficits that may represent biomarkers for the eventual onset of prodromal psychosis in 22q11DS.

Finally Dr. Michaelovsky will present the results of bioinformatics analyses on DNA samples of a unique 22q11.2DS multigeneration family (mother and her four children), including psychotic and non-psychotic subjects.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.565

PSYCHOSIS RISK IN 22Q11.2 DELETION SYNDROME: FINDINGS FROM THE PHILADELPHIA SAMPLE

Raquel Gur[1], James Yi[2], Sunny Tang[1], Monica Calkins[1], Tyler Moore[1], James Schmitt[1], Donna McDonald-McGinn[2], Elaine Zackai[2], Michael Xie[2], Ruben Gur[1], Beverly Emanuel[2]

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Abstract

Aim: Schizophrenia research emphasizes identification of people at risk of psychosis. 22q11DS, associated with increased risk for schizophrenia, is a window for studying emerging psychosis. Such efforts require systematic evaluation of subthreshold psychotic symptoms that can inform the general population. Our goal is to compare youths with 22q11DS to non-deleted youths with similar clinical features. We also examined comorbidity for psychiatric disorders, neurocognitive profile and, neuroimaging in a subsample.
Methods: 150 youths with 22q11DS and 150 non-deleted youths (9-24 years) matched on age and sex, stratified for presence of psychosis-spectrum features were evaluated for psychosis (SIPS) and other psychopathologies. Youths and caregivers were evaluated separately. Consensus ratings were analyzed with item-wise comparisons, factor analysis, and differential item functioning. The Penn computerized neurocognitive battery was administered and 3T imaging obtained for a subsample.
Results: Subthreshold psychotic symptoms were common, with 85% of youths with 22q11DS endorsing one or more symptoms. Most commonly rated items were ideational richness (47%) and trouble with focus and attention (44%). Similar to non-deleted samples, factor analysis showed a 3-factor solution with positive, negative and disorganized components. Youths reported more positive symptoms and caregivers more negative symptoms. For equivalent overall symptom severity, youths with 22q11DS were significantly more likely than non-deleted to have impaired tolerance for stress. Neurocognitive deficits were evident and decreased brain parameters that may be linked in GWAS to genes implicated in schizophrenia.
Conclusion: Subthreshold psychotic symptoms are common with variable manifestation. Comorbidity, cognitive deficits and aberration in brain parameters are evident and may be associated with genes implicated in schizophrenia. Longitudinal studies are essential as well as larger scale studies.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.566

TWELVE YEAR LONGITUDINAL TRAJECTORIES OF NEUROANATOMY, FUNCTIONAL CONNECTIVITY AND NEUROPSYCHOLOGICAL FUNCTION IN 22Q11.2 DELETION SYNDROME: PREDICTION TO PSYCHOSIS

Wendy Kates[1], Seetha Ramanathan[1], Wanda Fremont[1], Ioana Coman[2], Leah Mattiaccio[1], Stephen Faraone[1], Kevin Antshel[3]

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[3]*Syracuse University*

Abstract

We conducted a twelve-year longitudinal study of neuroanatomic, neurofunctional and neuropsychological development in youth with 22q11.2 deletion syndrome (22q11DS). Participants, consisting of 88 youth with 22q11DS, 33 unaffected siblings, and 32 community controls, were recruited to our academic medical center from throughout North America, and were followed every three years for four timepoints. Mean age in years at the first timepoint was 11.9; second timepoint, 15.1; third timepoint, 18.1; fourth timepoint, 21.2. High resolution MRI scans and standard neuropsychological measures were administered at all timepoints. Trajectories of cortical thickness and surface area were measured with FreeSurfer, V.5.1. Functional connectivity (at the fourth timepoint only) was measured with the Functional Connectivity Toolbox (CONN) in Matlab. Positive symptoms of psychosis were measured with the Positive Symptom Subscale of the Structured Interview for Prodromal Symptoms (SIPS). Longitudinal linear mixed model regression analyses were conducted, and results were corrected for multiple comparisons. Relative to controls, probands displayed significantly slower rates of longitudinal change in cortical thickness of the superior parietal lobule and precuneus (p-values <0.01). Moreover, functional connectivity between superior parietal lobule and temporal regions were disrupted in probands relative to controls ($p < 0.02$). Parietal lobe trajectories also predicted Time 4 positive prodromal symptoms ($p<0.01$) in the probands. Over time, probands also exhibited slower rates of improvement in scores on visual working memory ($p=0.001$) and auditory/verbal learning ($p=0.002$) relative to their peers. Decrements in auditory/verbal learning were associated with Time 4 positive prodromal symptoms ($p=0.01$), as were decrements in the executive skill of set-shifting ($p=0.001$) and in sustained attention ($p=0.006$). We conclude that aberrant longitudinal alterations in parietal cortical thickness / connectivity, as well as decrements in auditory/verbal learning, executive function and sustained attention may represent biomarkers for the eventual onset of prodromal psychosis in 22q11DS.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.567

THE POTENTIAL ROLE OF GENETIC AND IMMUNOLOGICAL PATHWAYS IN 22Q11 DELETION SYNDROME PSYCHOSIS

Doron Gothelf

Sheba Medical Center

Abstract

The 22q11 deletion syndrome (22q11DS) is a neurodevelopmental condition associated with medical diseases, cognitive deficits and psychiatric morbidity. The common 3Mb 22q11 deletion contains ~40 genes. The 22q11DS has multiple potential medical manifestations including cardiovascular and cleft anomalies, hypocalcemia and thymic hypoplasia resulting in an increased risk for recurrent infections and autoimmune disorders. The most common and debilitating manifestations in 22q11DS are the cognitive deficits and psychiatric morbidity. The average IQ in 22q11DS is 75, within the borderline range. Psychiatric rate of psychiatric comorbidities in 22q11DS is ~70% with up to one-third of individuals fulfilling criteria for schizophrenia by adulthood.

We will present data from our group exploring the potential association between 22q11DS-psychosis and its related cognitive and neurophysiological deficits and variants of the COMT and PRODH, two genes from the 22q11-deleted region. These findings will be discussed in the context of the data reported from other laboratories on the genotype-schizophrenia phenotype in 22q11DS.

We will also report preliminary findings on the potential role of neuroinflammatory factors in 22q11DS psychosis. We found elevated levels of the neuroinflammatory factors CRP and IL-6 in 22q11DS psychotic patients. Taken together with recent promising genetic-immunological pathways from schizophrenia in the general population, our findings suggest that 22q11DS is a promising model to test the genetic-immunological pathways leading to schizophrenia.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.568

DETECTION OF RISK GENES FOR PSYCHOSIS IN A FAMILY WITH 22Q11.2DS - PRELIMINARY FINDINGS

Elena Michaelovsky

Felsenstein Medical Research Center

Abstract

The 22q11.2 deletion syndrome (22q11.2DS) is the most common microdeletion syndrome in humans. It is a multisystem congenital anomaly disorder characterized by

variable manifestations including high rates of neuropsychiatric disorders. A unique 22q11.2DS multigeneration family was studied. Variability of psychiatric phenotypes in the affected family members (mother and her four children), including psychotic and non-psychotic subjects, enabled us to attempt to identify genetic risk factors that contribute to psychotic disorder and schizophrenia (SZ). Comparative genomic hybridization (CGH) array identified 15 CNVs outside the 22q11.2 region, and two of them defined as rare. De novo CNVs were detected only in the severe psychotic siblings (SZ and delusional disorder). These findings support the de novo mutation theory of SZ.

The 22q11.2 haplotype analysis based on whole exome sequencing (WES) identified two haplotype variants for the four 22q11.2DS siblings: one for the three psychotic siblings termed by us as a "psychosis" risk haplotype and the other for the non-psychotic sister, a putative "protective" haplotype. WES enabled us to search for additional genetic variants outside 22q11.2 region using two approaches: 1) search for de novo mutations and recessive alleles for the SZ individual; 2) search for variants that are common to the psychotic siblings as well as variants that are unique to the SZ individual, using the Venn model.

Bioinformatic analyses of CGH array, WES and 22q11.2 haplotype construction resulted in identifying de novo, rare, conserved and "damaging" genetic variants involved in cellular pathways relevant to neurodevelopmental disorders that may contribute to the psychotic phenotype in this 22q11.2 family.

Such multi-affected families with phenotypic variability can assist in identification of genetic risk variants that contribute to the susceptibility to develop psychosis in 22q11.2DS that may also be relevant to SZ in general.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.569

Tuesday, November 1, 2016 15:45 - 17:30 Oral Session: Mood Disorders - Genetic Studies of Etiology, Pathogenesis, and Treatment

POLYGENIC RISK, EARLY ADVERSE LIFE EVENTS AND DEPRESSION IN THE IPSYCH COHORT

Katherine Musliner[1], Gry Poulsen[2], Esben Agerbo[3], Veera Manikandan[4], Preben Bo Mortensen[1], Merete Nordentoft[5], Michael Benros[5], Wes Thompson[6], Trine Munk-Olsen[7], Nis Suppli[5]

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Background: Major depressive disorder (MDD) is moderately genetic, with population-based heritability estimates of 30-40% and SNP-based heritability estimates of 20-25%. However, a large proportion of risk for MDD is attributable to the environment. Early adverse life events (EALEs), such as the death of a parent, are well-established risk factors for MDD. Candidate gene studies indicate that EALEs interact with single genes to influence MDD risk. However, mounting evidence suggests that the underlying genetic architecture of MDD is polygenic. To date, only two studies have examined whether polygenic risk (PR) interacts with early adversity to predict MDD. Peyrot et al. (2014) found in the NESDA study that the effect of PR on MDD was stronger among individuals with a history of childhood trauma. Mullins et al. (2016) found the opposite: among people with moderate/severe trauma, the log odds of MDD decreased as PR increased. The goal of this study is to evaluate the extent to which EALEs interact with PR to predict MDD in the Danish iPSYCH cohort. The iPSYCH cohort contains 88,764 individuals, including 24,693 MDD cases, making this by far the largest study on the topic to date.
Methods: The iPSYCH cohort has a case-cohort design, containing individuals randomly sampled from the population of people born in Denmark between May 1, 1981-Dec 31, 2005, along with additional psychiatric cases identified from the Danish Central Psychiatric Research Register. DNA was extracted from dried blood spots and amplified in triplicate. Individuals were genotyped using the PSYCH chip. In this study, we will use data from controls and cases with an MDD diagnosis (ICD-10 codes F32, F33). EALEs, including death of a parent, death of a sibling, parental hospitalization, parental imprisonment, parental unemployment, parental divorce/separation, foster care and abuse, will be assessed using information from other Danish nationwide registers. EALEs will be operationalized as a weighted count variable of the number of events experienced by each individual before the age of 15. PR scores will be calculated using the PGC2 MDD results (not including the iPSYCH sample) as the training dataset (Purcell, 2009). Statistical analyses will be conducted using Cox Proportional Hazards

Models, with weights to account for the case-cohort design (Self & Prentice, 1988).
Results: The PR scores which will be used in this study are currently being finalized. We anticipate that this process will be finished in August, 2016, which will give us over two months to conduct the analyses and prepare the results for presentation at the WCPG conference.
Discussion: Pending finalization of results.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.570

POLYGENIC RISK SCORES REVEAL PATTERNS OF ASSORTATIVE MATING AND ANTICIPATION IN A LARGE PEDIGREE AFFECTED WITH MOOD DISORDERS

Simone de Jong[1], Mateus Jose Abdalla Diniz[2], Andiara Calado Saloma Rodrigues[2], Ary Gadelha[2], Marcos Santoro[2], Vanessa Ota[2], Christiano Noto[2], Charles Curtis[1], Hamel Patel[1], Lynsey Hall[3], Paul O'Reilly[1], Sintia Belangero[2], Rodrigo Bressan[2], Gerome Breen[1]

[1]*King's College London*
[2]*Universidade Federal de São Paulo (UNIFESP/EPM), São Paulo, Brazil*
[3]*Newcastle University, Newcastle upon Tyne, United Kingdom*

Background: Psychiatric disorders are leading causes of disability globally. Worldwide prevalence rates for mood disorders range from around 1% for Bipolar disorder (BP) to 5.7% for Major Depressive Disorder (MDD). Having a first-degree relative with a psychiatric disorder is a significant risk factor for developing the same or a related psychiatric disorder, and heritability estimates range from moderate for MDD (~40%) to high for BP (80-90%). This indicates a significant genetic component in their etiology, which is likely comprises a combination of rare and common genetic variation. The aim of this study is to examine the role that common genetic variation confers on disease risk in a severely affected pedigree that would have traditionally been viewed through the prism of monogenic inheritance only.
Methods: To achieve this we exploit both a large pedigree (n~300) with high prevalence of mood disorders (30% of family members is affected with major depressive disorder (MDD) or bipolar disorder (BP)) and the recently popular polygenic risk score (PRS) approach. Illumina Psych chip data is available for 243 family members of which 78 individuals are affected with mood disorders (including 36 BP and 38 MDD patients) and 57 unrelated healthy Brazilian controls. Using psychiatric PRS derived from recent large GWAS mega analysis efforts in psychiatric disorders like schizophrenia (SCZ), BP and MDD, we examine patterns of assortative mating and anticipation in the family.
Results: First, we examine common variant effect on risk via an association between PRS and case/control status in the pedigree. Next we investigate an increase in PRS value across the generations, seemingly driven by the transmission of elevated PRS to offspring from 46 affected married-in individuals. This suggests that PRS contributions from married-in individuals, caused by assortative mating on phenotype, may increase risk for psychiatric disorders beyond that conferred by rare variation transmitted from within the family.
Discussion: Leveraging results from the SCZ2 mega analysis into PRS allowed us to investigate the relationship between common genetic variation and patterns of assortative mating and anticipation in a complex multigenerational pedigree affected with mood disorders. A joint analysis of both rare and common variation may be the most powerful way to understand the familial genetics of mood and psychiatric disorders.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.571

GENETIC INFLUENCES ON INFLAMMATORY BIOMARKERS IN BIPOLAR DISORDER

Sarah Bergen[1], Erik Pålsson[2], Anniella Isgren[2], Jie Song[3], Joel Jakobsson[2], Mikael Landen[2]

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Background: Inflammatory mechanisms have been implicated in the pathophysiology and progression of bipolar disorder. Markers of inflammation circulating in blood are often used in these investigations, but demonstrate little relationship to central nervous system inflammation and related biomarkers in the cerebrospinal fluid (CSF). This study investigates the genetic mediation of inflammation biomarkers in CSF and serum from subjects with bipolar disorder and healthy controls.
Methods: Subjects were drawn from the St. Göran Bipolar Project which enrolls patients from bipolar disorder clinics in Gothenburg and Stockholm in addition to age and sex-matched healthy controls. For the inflammation-related biomarkers YKL40, MCP1, sCD14, TIMP1, and TIMP2, CSF and serum levels were quantified, as well as CSF levels of IL8 and serum levels of CRP and MMP9. Subjects were genotyped using the Affymetrix 6.0 and Illumina OmniExpress arrays. Genome-wide association studies of these biomarkers were conducted for the 51-57 controls and

101-164 cases with available data using PLINK and included covariates for age, sex, and principle components accounting for population substructure.
Results: Genome-wide significant associations ($p<5x10-8$) resulted from all analyses with the exception of CSF derived levels of TIMP1. Multiple genomic regions exert regulatory effects for the majority of biomarkers tested, but there was little concordance between associated regions for CSF and serum-derived measures when both were available for a given biomarker.
Discussion: Levels of inflammatory biomarkers in CSF and serum are both genetically mediated but probably differentially. The associated genetic markers, in conjunction with the biomarker levels previously associated with bipolar disorder, could be used to aid diagnoses and as possible targets for the development of novel therapeutics.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.572

GENOME-WIDE GENE EXPRESSION SIGNATURE OF DEPRESSION

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Background: Many studies have attempted to identify the molecular signature of depression. The results, however, are inconsistent. The small sample sizes, choice of tissue/cell types and suboptimal statistical methods are the major limitations that might contribute to this inconsistency. In our study, to identify the whole blood transcriptome signature of geriatric depression, we utilized two large population cohorts aged over 65 -The Sydney Memory and Aging Study, MAS ($N=521$) and The Older Australian Twin Study, OATS ($N=324$) as discovery and replication cohorts, respectively. Major Depression was assessed according to DSM-IV criteria.
Methods: The genome-wide gene expression data were obtained using Illumina HT-12 v4. After quality control and pre-processing, the application of stringent filtering criteria (by detection p-value ($p<0.01$ in $\geq 50\%$ of samples) and coefficient of variation (0.01)) resulted in 11,018 top-varying genes for downstream analyses. Using the Weighted Gene Coexpression Analysis (WGCNA), we constructed a network consisting of 29 modules. The relationship between the eigengenes of each module (principal components) as well as the other genes within the individual modules and the phenotype of depression was assessed using correlational analyses. The measures of gene significance (GS) and module membership (MM) were used to identify the genes relevant to depression.
Results: The eigengenes of two modules were associated with the depression phenotype ($p=0.01$ and $p=0.02$). Closer inspection of the modules of interest revealed that only 37 out of 82 genes in one module and 17 out of 64 genes in another module were significantly associated with the phenotype of depression. Correlational analyses of individual genes within the depression relevant modules revealed that 8 out of 37 significant genes in one module were protein coding genes, involved in various translational, metabolic and immune processes (PCYOX1L, RPL14, MCTS1, GIMAP7, NDUFB9, BOLA2, EIF3M, RPL7A). The second module contained 5 protein coding genes out of 17 associated with depression, the known molecular functions of which include catalytic, enzyme regulation, transcription factor and translational regulation activities (PRCP, POLR2J2, ATF4, TAOK3, EIF2B5). The two top genes from both modules are known to be involved in metabolic process regulation by reactive oxygen species (PCYOX1L, prenylcysteine oxidase-like ($p<0.001$) and PRCP, prolylcarboxypeptidase ($p<0.05$)). A replication study is underway in a sample of 324 subjects of similar age, gender, and ethnicity.
Discussion: Our results support the oxidative stress hypothesis of depression and provide new insights into pathophysiological mechanisms of geriatric depression. In addition, we will present the results from pathway analyses (Ingenuity Pathway Analysis software, IPA) performed on genes identified as relevant to depression in this study. To bridge genotype with whole blood transcriptome and identify genomic loci that influence the identified gene expression signature of depression, we will present results from genome-wide eQTL analyses, which are ongoing.

Disclosure

Nothing to Disclose.

http://dx.doi.org/10.1016/j.euroneuro.2016.09.573

CONDITIONAL KNOCKOUT OF ANKYRIN-G IN THE MOUSE FOREBRAIN RESULTS IN BIPOLAR-LIKE BEHAVIOR

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Background: To date, few animal models of bipolar disorder have been developed, and fewer still are based on genetic loci despite the fact that genome wide association studies (GWAS) have now identified a number of candidate genes. Across studies, one of the most consistent findings is in ANK3, which encodes Ankyrin-G, a protein that organizes sodium and potassium channels at the axon initial segments (AIS). To explore the potential pathophysiological role of Ankyrin-G in bipolar disorder, we generated a mouse model with conditional deletion of all major isoforms of Ank3 in the adult forebrain.
Methods: Ank3 flox mice (Ank3 flox/flox) were crossed with Camk2a-Cre mice, which begin to express Cre in the forebrain at post-natal day 19. Beginning at 3 months of age, the behaviors of conditional knockout mice and control littermates were assessed in a 24 hour locomotor activity test, open field, elevated plus maze, forced swim test, and prepulse inhibition test. In a second cohort, behavioral effects of two mood-stabilizers, lithium and valproic acid, as well as the stimulant methylphenidate were assessed. In separate cohorts, mice were exposed to 14 day cycles of social defeat stress, a commonly used paradigm that results in a depression-like phenotype among wild-type mice. Finally, the behavior of heterozygous mice was characterized at baseline and then after exposure to social defeat stress and treatment with the antidepressant fluoxetine.
Results: Conditional knockout of Ank3 (cKO) resulted in striking hyperactivity, sleep-cycle disruption, and decreased anxiety-like behaviors. Ank3 cKO mice were indistinguishable from controls in prepulse inhibition, where deficits are often found in models of schizophrenia. Consistent with a mania-like phenotype, the hyperactivity of Ank3 cKO mice was normalized by treatment with lithium and valproic acid. When treated with methylphenidate, both Ank3 cKO and control mice displayed increased locomotor activity. After 14 days of social defeat, Ank3 and control mice displayed a depression-like phenotype. Consistent with a bipolar depression-like phenotype, Ank3 cKO mice expose to social defeat were indistinguishable from socially defeated controls. When allowed to recover for 14 days and then re-exposed to social defeat, Ank3 cKO mice, but not controls, displayed evidence of 'cycling' between mania and depression-like behaviors. Finally, we found that Ank3 heterozygous mice are indistinguishable from controls at baseline. However, Ank3 heterozygous mice appear to be more sensitive to both social defeat stress and the antidepressant fluoxetine.
Discussion: Overall cKO of Ank3, a genetic loci that has repeatedly been implicated in human bipolar disorder and is involved in organization of the axon initial segment, recapitulates major aspects of both bipolar mania and bipolar depression. We believe that this novel genetic model may provide a better understanding of the role of of Ankyrin-G in the brain, further insights into the molecular biology of bipolar disorder, and allow for the development of novel therapeutic approaches.

Disclosure

Nothing to Disclose.

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THE PHARMACOGENOMICS OF BIPOLAR DISORDER STUDY: A COMBINED ANALYSIS OF IPS NEURONAL EXPRESSION AND GWAS DATA IDENTIFIES CBARP AND CARD19 AS ASSOCIATED WITH LITHIUM RESPONSE

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Background: Lithium was the first mood stabilizing medication and remains the most effective. A variety of data argue that lithium responsive bipolar disorder may be genetically distinct and hence lithium response may be a powerful probe distinguishing different forms of illness. The Pharmacogenomics of Bipolar Disorder study has recently completed a prospective trial of lithium in order to quantify lithium response in 585 subjects with bipolar I disorder and conducted a GWAS on this sample. We have also recently reported that iPS derived glutamatergic hippocampal neurons demonstrated a 4 fold

higher spontaneous firing rate that was reversed by lithium, but only in cells from lithium responders. Realizing that it was very difficult to obtain GWAS-size samples from a prospective trial, the PGBD study was originally designed to use functional data from stem cell derived neurons in order to reduce the number of statistical tests.

Methods: 11 sites participated in a 2.5 year prospective trial of lithium in bipolar I subjects. After written informed consent and 4 months of stabilization, subjects were followed for 2 years on monotherapy. Response was quantified as time to relapse. 585 subjects were genotyped using the Illumina PsychArray. A pilot GWAS of 321 European American subjects was conducted using plink and principal components from ancestry markers. RNAseq was conducted on all the iPS experiments in which lithium or control was applied to hyperexcitable cells. Expression was analyzed and compared using EdgeR in the Bioconductor package.

Results: Genes were selected from the iPS RNAseq data that underwent a significant change in expression in response to lithium, but only in cells from lithium responders. This yielded a list of 469 genes which were then compared with brain eQTL databases. 143 of these genes had known variants affecting expression in brain. Of these 143 SNPs, 27 were directly genotyped. The GWAS p values for these 27 SNPs were examined and one SNP was identified (rs621071) on chromosome 1 that regulates a gene on chromosome 9 (CBARP) and a gene on chromosome 19 (CARD19). This SNP showed significant association to lithium response after Bonferroni correction for the much smaller number of tests ($p=0.026$).

Discussion: The combined analysis of GWAS and functional studies make possible genomewide analyses of smaller more difficult to phenotype samples. CBARP is a very interesting candidate that binds to CACNA1C and modulates current through L-type voltage gated calcium channels as have been implicated in bipolar disorder. The function of CARD19 is less clear but may involve inhibition of Bcl-10. Lastly, these results suggest that drug response may be a powerful phenotype with which to dissect different cellular mechanisms in bipolar disorder.

Disclosure

Nothing to Disclose.

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POLYGENIC SCORES DERIVED FROM NEUROIMAGING ENDOPHENOTYPES PREDICT OUTCOMES TO PSYCHOTHERAPY AND MEDICATION TREATMENTS FOR MAJOR DEPRESSIVE DISORDER

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Background: Biomarkers to guide optimal treatment selection are lacking for major depressive disorder (MDD). Despite some promising findings, candidate gene and genome-wide association studies (GWAS) of antidepressant response have met with little success and none has focused on differential outcome to mechanistically different treatments. Development of such biomarkers would allow to better match patients with their most favourable treatment and has direct implications for the development of precision biology-based clinical practice.

Methods: The overall aim of this work is to provide a framework for developing easily accessible predictors of individualized treatment response. Using a neuroimaging-based genomics approach, we investigated whether polygenic scores (PGS) derived from single nucleotide polymorphisms (SNPs) influencing hippocampus (HC) volume from the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) study (Hibar et al., 2015) could predict treatment-specific outcome in an independent cohort; the Prediction of Remission in Depression to Individual and Combined Treatments (PReDICT) sample (B. W. Dunlop et al., 2012). PReDICT enrolled treatment-naïve patients and randomized them to three antidepressant treatments; CBT, ESC and duloxetine (DUL). As such, it is the largest single-site MDD randomized trial comparing CBT to antidepressant medication (ADM) ever performed.

Results: HC-PGS predicted differential outcomes ($P = 0.00053$ and $R2 = 4.6$) to CBT vs. ADM in PReDICT. In addition after predicting randomly permuted response status 1000 times with the best-fit HC-PGS, only one P-value was lower than those initially achieved ($pperm < 0.0009$). Genes tagged by SNPs from neuroimaging-based predictive PGS were enriched for cortical and striatal brain cell-type specific expression patterns ($PBonferroni = 0.013$).

Discussion: The approach used in this work contributes to the identification of molecular pathways possibly critical for antidepressant outcomes and offers novel insights into MDD pathophysiological subtypes. We demonstrate that combining neuroimaging and genetic markers is essential to identify predictors of antidepressant response and may allow selection of a specific treatment for specific patients.

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Oral Session: Novel Approaches to Genetic Studies in Schizophrenia and Related Phenotypes

NOVEL BIPOLAR AND SCHIZOPHRENIA RISK GENES IDENTIFIED THROUGH GENIC ASSOCIATIONS IN TRANSCRIPTOME IMPUTATION

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Background: Genome-wide association studies (GWAS) have identified genomic regions harboring GWA-significant common variation. Undoubtedly many more remain to be identified. Large-scale transcriptomic datasets have pinpointed variants regulating gene expression (eQTLs) in specific tissues; moreover, these results can be used to impute tissue-specific gene expression levels (GREx) for any genetically-characterized sample. Building from these observations, recent research has pointed out that imputed gene expression in larger case-control samples can be tested to identify novel risk genes. Here, we use the largest existing transcriptomic database of brain tissue, along with data from ten GTEx brain regions, to impute GREx and test for association in GWAS datasets of schizophrenia (SCZ) and bipolar disorder (BIP) from the Psychiatric Genomics Consortium (PGC).

Methods: Following systematic comparison of prediction modelling techniques, models were created for 13,452 genes from 668 individuals with imputed genotype and RNA-seq data from the CommonMind Consortium(CMC). GREx was imputed in a novel cohort of ~400 individuals and had good prediction accuracy (~85% of genes have R2 0.01-0.5), in line with previous models and results. Our results were compared across ancestries and to individual- vs. summary-level data.

Our analysis used CMC and 17 GTEx models to impute GREX in PGC SCZ (~34,000 cases/45,000 controls) and BIP (~20,000/31,000). Models corresponded to 10 brain regions, 6 heart tissues, and a whole blood sample. We tested imputed GREX for association with SCZ and BIP.

Results: We identified 302 genes with genome-wide significant ($p < 5x10-6$) associations in SCZ, and 105 in BIP. For both disorders, we identify novel genic associations, and validate findings from similar genic association studies. Moreover, we identify a number of well-established SCZ and BIP loci; of the 108 SCZ PGC GWAS loci, 74 had at least one associated gene reaching nominal significance in this study, while 27 reached genome-wide significance. In BIP, 54/75 top loci ($p < 1x10-6$) have a gene reaching nominal significance, and 11 reached genome-wide significance. For both disorders, roughly half of these associations lie in the MHC region, which may help elucidate the complex local landscape of disease risk.

Discussion: We have used GREx imputation to harness large GWAS sample sizes and yield biologically relevant data about disease architecture, resulting in the first prediction models for the DLPFC. These predictors may identify novel genic associations, as shown for BIP and SCZ. We will expand on these analyses to probe the general relationship between GWAS-loci, differential gene expression, and eQTLs. We will further use these predictors to address questions about the role of gene expression in disease risk and heritability.

Disclosure

Nothing to Disclose.

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ASSOCIATION OF THE POLYGENIC RISK SCORE FOR SCHIZOPHRENIA WITH MORTALITY AND SUICIDAL BEHAVIOUR - A DANISH POPULATION-BASED STUDY

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Background: People who suffer from schizophrenia have a 15-20 year shorter life expectancy and are at increased risk of committing a suicide attempt. Adverse effects of family histories of mental disorders, sedentary lifestyles, side effects of medical treatments, and insufficient somatic treatments are contributing factors. However, it is unknown whether an increased genetic liability to schizophrenia influences the risk of dying early and commenting a suicide attempt.

Our objectives was to determine whether the genetic predisposition to schizophrenia is associated with the risk of dying early and experience a suicide attempt.

Methods: Design and Settings: Case control study.

Setting: Denmark.

Participants: Cases diagnosed with schizophrenia in the period 1994-2008 who were born after 1982($n = 1780$) and 1768 matched population-based controls.

Exposure: The polygenic risk score for schizophrenia

Main Outcomes and Measures: The outcome of interest was death and suicide attempts in cases and controls. The main measure was the mortality rate ratios (MRR) for deaths and odds ratios (OR) for multiple suicide attempts, associated with one standard deviations increase of the polygenic risk score for schizophrenia (PRS).

Results: We replicated the high mortality MRR = 9.01 (95% CI: 3.56-22.80), and high risk of multiple suicide attempts OR = 33.16 (95% CI: 20.97 – 52.43) associated with schizophrenia compared to the general population. However, there was no effect of the PRS on mortality MRR = 1.00 (95% CI 0.71-1.40) in the case-control setup or in cases only MRR = 1.05 (95% CI 0.73 - 1.51). Similar, no association between the PRS and multiple suicide attempts was found in the adjusted models, but in contrast, family history of mental disorders was associated with both outcomes.

Discussion: A genetic predisposition for schizophrenia, measured by PRS, has little influence on the excess mortality or the high risk of suicide attempts. In contrast there is a strong significant effect of family history of mental disorders. Therefore, the excess mortality may more likely be attributable to modifiable factors connected to growing up or living in a family with mental disorders, and more general modifiable risk factors such as inadequate somatic treatment and sedentary life lifestyles. However, our sample was only of limited size

Disclosure

Nothing to Disclose.

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HIGHER GENETIC RISK FOR SCHIZOPHRENIA IS ASSOCIATED WITH LIVING IN URBAN AND POPULATED AREAS

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Background: The prevalence of schizophrenia is higher in urban areas than in rural areas. The association between urbanization and schizophrenia has been reported before in relation to place of birth, place of upbringing and place of residence. Two major hypotheses have been proposed to explain this phenomenon: (1) the causation hypothesis, where the stress of city life and undefined factors in the urban environment would increase the risk of this disease, and (2) the selection hypothesis, where individuals with genetic liability for schizophrenia would move into urban areas.

On the other hand, genetic factors have been shown to have a higher impact on the country v.s city living as people grow older (>40y), while the impact of family background decreases. Heritability estimates reported for full ACE models were 12.7%, 22% and 41.2% for those under 20, 20-40 and over 40, respectively.

Our aim was to test the alternative hypothesis that adults with higher genetic risk for schizophrenia are more likely to move to and live in urbanized and populated areas than those with lower risk.

Methods: Our sample was comprised of 15,253 participants in 7,007 families (63.4% women) over 40 years old (M = 54.43, SD = 10.86) living in Australia. The participants reported their postcode as part of the protocols of several studies on health and wellbeing conducted from QIMR. Participants were genotyped genome-wide and imputed to 1000G v.3.

We used three measures of urbanicity; (i) subjects' zip code were categorized into urban, suburban or rural zones; we also computed (ii) distance to the closest city centre and (iii) the population density of the postcode district. Polygenic risk scores (PRS) for schizophrenia based on summary statistics from the Psychiatric Genomics Consortium (PGC-2) were computed with PLINK 1.90 (version 3) for eight different P-value thresholds. We used linear mixed models to predict the three urbanicity measures from the schizophrenia PRS, controlling for age, sex, genetic principal components, GWAS chip and genetic relationship matrix. Predictions were calculated using GCTA (Genome-wide Complex Trait Analysis, version 1.22).

Results: Genetic risk for schizophrenia was associated with the place where the participants lived in the expected direction, with increased effects as the risk scores included more SNPs.

P-values for PRS at thresholds <0.05 were 7.02*10-5 , 4.75*10-2 and 9.78*10-6, for zone, city distance and population density respectively while for threshold P<1 they were correspondingly 4.75*10-7 , 1.2*10-3 and 1.19*10-6.

Discussion: Our results suggest that people with a higher genetic risk for schizophrenia may prefer to live in more urban and populated areas. Importantly, this study does not use a case-control sample but a non-selected sample where the genetic risk for schizophrenia was estimated.

This study proposes that greater genetic predisposition to schizophrenia is at least one mechanism explaining why this illness is more prevalent in city environments. Future research should test if this effect is replicated in other countries.

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Disclosure

Nothing to Disclose.

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GENOME-WIDE ASSOCIATION STUDIES OF SMOOTH PURSUIT EYE MOVEMENTS ACROSS PSYCHOTIC DISORDERS: PRELIMINARY FINDINGS FROM THE B-SNIP SAMPLE

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Background: Smooth pursuit eye movement dysfunctions are regarded as intermediate phenotypes for psychotic disorders. They include first, impairments of sensorimotor processing during pursuit initiation and second, deficits of sustained pursuit maintenance implicating different functional brain systems. Here we were interested in genetic alterations specifically related to these pursuit deficits.
Methods: Pursuit performance was assessed in 849 participants (schizophrenia N=230, schizoaffective disorder N=155, psychotic bipolar disorder N=206, and healthy controls N=258) of the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. Participants were 18-65 years of age and without significant neurological disorder, recent substance abuse or dependence. A mixed modeling GWAS approach (EMMAX) was performed using genotyping assessed with the PsychChip (287,637 SNPs with MAF>0.01 passing standard GWAS QC criteria). Eye acceleration (measure of sensorimotor processing) and sustained maintenance gain (measure of cognitive control) were modeled as quantitative trait phenotypes in relation to genetic data while controlling for genetically-derived ancestry measures, age, and sex. Probands and controls were grouped together for primary analyses stratified by the top two genetically-derived ancestry groups with follow-up studies in proband or control categories.
Results: Genome-wide associations ($p < 5x10\text{-}8$) with sensorimotor processing deficits were identified with SNPs in IPO8 (ch12), PCDH12 (ch5), and CABLES1 (ch18) for participants with predominating African ancestry. Follow-up analyses showed that these associations were predominantly driven by psychosis probands. Sensorimotor deficits were also associated with a SNP in CYB5R3 (ch22) for participants with predominating Caucasian ancestry. Suggestive associations with sustained pursuit maintenance were identified in two genes on chromosome 9 (ACTL7A and TTC16) as well as the TMPRSS5 gene on chromosome 11.
Discussion: Protocadherin 12 (PCDH12) encodes a member of the cadherin family of proteins previously identified for involvement in neurodevelopment and brain morphology in both schizophrenia and bipolar disorder. By disturbing fast axonal guidance and synaptic specificity, variation in this gene may impact neuronal signaling needed for sensorimotor processing. CABLES1 encodes a protein involved in cell cycle regulation and has been identified as an important component of neural development and interhemispheric connections needed for predictive control of sustained pursuit. Relationships between neurodevelopment related genes and smooth pursuit genotypes represent novel findings that may give insights into the behavioral/neurophysiological consequences of genetic variation in these systems and its alterations in severe mental illness. Other genes implicated in our association studies represent novel relationships requiring further study.

Disclosure

Nothing to Disclose.

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PSYCHIATRIC GENOMICS CONSORTIUM – GENETIC ARCHITECTURE OF SCHIZOPHRENIA IN ASIAN POPULATIONS

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Background: During the past years, significant progress has been made to understand the genetic architecture of schizophrenia, with 108 loci spanning across the human genome demonstrated to be significantly associated with the illness. To date, there have been several follow-up reports investigating the biological functions of these loci and their impact on schizophrenia. Nevertheless, a majority of previously reported samples were of European descent, and it is currently unclear whether the genetic architecture of schizophrenia across populations would be similar. Here we present the PGC schizophrenia Asia initiative, a large-scale schizophrenia genetics study to systematically examine the schizophrenia genetic architecture in the non-European population.
Methods: Schizophrenia cases and controls from Singapore, Hong Kong, Taiwan, mainland China, Japan, and Indonesia are consolidated for the Asian genome-wide association analysis. A total sample size of N = 42,400 (Ncases=17,400; Ncontrols=25,000) are projected for analysis. Standard quality control procedures for genome-wide analysis are carried out via the Ricopili pipeline. Population outliers are examined via principal components analysis. Imputation for each cohort is carried out for the 1000 genomes phase 3 reference panel.
Results: Planned Analysis: Heterogeneity analysis will be conducted via meta-analytic and mega-analytic approaches

and compared against summary statistics of Ncases= 33,640; Ncontrols=43,456 European-descent samples from the most recent PGC SCZ meta analysis. Genetic correlation between European and Asian schizophrenia will also be conducted using popcorn, a version of LD regression that allows cross-population comparisons.
Discussion: The current effort to examine the genetic architecture of schizophrenia in Asian subjects aims to inform if the biological underpinnings of schizophrenia are different across the population, fine-map known loci and allow further novel loci associated with schizophrenia to be discovered through deep replication.

Disclosure

Nothing to Disclose.

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FINDINGS FROM CONTINUING GENE HUNT IN FAMILIES WITH SCHIZOPHRENIA

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Background: Schizophrenia (SZ) is a common psychiatric disorder with a large genetic component but perceptible heterogeneity. This together with lesser known etiological environmental cues makes the study of this illness a continuing challenge globally. Association studies of common variants in a range of candidate genes or genome-wide, in sporadic SZ cohorts fail to explain total heritability paving way for newer strategies to be exploited. Among these, rare variant discovery and trans-ethnic studies are expected to hold promise. Further, familial forms of SZ with multiple affected members are hypothesised to harbor shared, rare but highly penetrant variants/mutations. This study focussed on investigating a few such families of Indian origin.
Methods: Of several patients/families diagnosed with SZ at Dr RML Hospital, New Delhi using DSM IV criteria and recruited following institutional ethical committee clearance and written informed consent, 25 families with three or more affected members were selected for whole exome sequencing. A minimum of three informative individuals from each of these families were sequenced using the Agilent V5+UTR exome target capture kit. Analysis of exome data and variant prioritisation were done using standard pipeline.
Results: We identified over eight rare variants including compound heterozygotes in previously reported and in novel, functionally relevant candidate genes segregating with disease in these families. Mutation screening in these genes among sporadic SZ cases of north Indian ancestry to assess their overall contribution to disease etiology is underway.
Discussion: Next generation sequencing technologies have greatly facilitated discovery genomics in both Mendelian disorders and complex traits. Besides likely improved insights into disease biology by ongoing pathway analysis, uncovering new disease associated genes may also offer an opportunity to identify potential novel therapeutic targets. These findings will be presented during the meeting.

Disclosure

Nothing to Disclose.

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WHOLE EXOME SEQUENCING IN ARAB AND JEWISH ISRAELI FAMILIES MULTIPLY AFFECTED WITH SCHIZOPHRENIA

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Background: Schizophrenia is a complex disorder that likely results from the impact of both common and rare susceptibility variants. The impact of common variants with small effect in schizophrenia has been widely investigated. After large scale sequencing studies in schizophrenia become feasible, multiple whole exome sequencing studies were performed, and found disruptive mutations distributed across many different genes. They also identified gene sets with enrichment of rare variants with large effect. Sequencing studies performed in large families have showed that candidate variants did not necessarily segregate within the families, and were different in each family. To search for inherited variants of large effect we performed whole exome sequencing in Arab and Jewish Israeli families multiply affected with schizophrenia. All the Jewish families were of non-Ashkenazi origin. The Arab families were drawn from an ethnically homogenous population with an unusually high level of consanguinity, and a low rate of intermarriage with other population groups in Israel.

Methods: Eight large families with multiple subjects affected with schizophrenia were selected, since in these families the genetic transmission appears to be most consistent with inheritance of highly-penetrant disease alleles. In total whole exome sequencing and data analysis of 32 family members were performed. Each family was analyzed separately, first according to the most appropriate single-gene mode of inheritance and second according to an oligogenic mode of inheritance looking for all variants shared between affected family members. Multiple variants found by applying the oligogenic mode of inheritance were prioritized by using the VarElect software. To assess enrichment of rare segregating variants in specific genes in the schizophrenia cases, we performed a gene-based collapsing dominant model analysis while correcting for population stratification. Permutation-based analyses were done to test for enrichment of previously detected de-novo variants and additional candidate gene sets.
Results: We were able to identify several interesting rare segregating functional variants. Single-gene inheritance candidates which are consistent with the most appropriate mode of inheritance in a given family were found in only 2 out of 8 analyzed families. These variants were found in DOCK8 and DRP2 genes. No gene reached genome-wide significance in the collapsing analysis. An enrichment of variants in candidate gene sets is currently under investigation.
Discussion: It seems that schizophrenia in most of these families arises from the combined effects of several different coding variants, even in ethnically homogenous consanguineous Arab Israeli families.

Disclosure

Nothing to Disclose.

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Oral Session: Unique Studies in Psychiatric Genetics

THE UK BIOBANK: A RESOURCE FOR CNV ANALYSIS

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Background: The UK Biobank is a unique resource for biomedical research, with extensive phenotypic and genetic data on half a million adults. We wanted to call all pathogenic CNVs in the first 150,000 participants and examine the cognitive performance and phenotypic characteristics of their carriers.
Methods: We used Affymetrix Power Tools and PennCNV-Affy software to analyse 152,728 Affymetrix microarrays in batches of ~4,600 from the first data release. We annotated a list of 93 CNVs that have been proposed to be pathogenic.
Results: The frequencies of the 93 CNVs were remarkably similar to those among 26,628 controls from other datasets. Carriers of neurodevelopmental CNVs performed worse on cognitive tests and had lower educational and occupational attainment. Carriers of CNVs with known phenotypes displayed the expected characteristics, e.g. increased or reduced BMI in 16p11.2 deletions and duplications carriers.
Discussion: The UK Biobank is the largest population study that allows the study of the effect of CNVs on cognitive and physical phenotypes. The set of CNVs will be made available for use by the scientific community.

Disclosure

Nothing to Disclose.

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COPY NUMBER VARIANT ANALYSIS OF PSYCHIATRIC TRAITS IN A COMMUNITY-BASED PEDIATRIC SAMPLE

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Background: Genetics play an important role in ADHD and OCD but only a handful of mostly common risk variants have been identified in studies that compare ADHD/OCD patients with healthy controls. Copy number variants of high penetrance may play an important role in childhood neuropsychiatric disorders. Our current knowledge of CNVs in ADHD and OCD is based on relatively small samples of patients, and to interpret the significance of these CNVs we need to assess risk CNVs in the general population. To this end we determine the frequency

of clinically relevant CNVs in a large population based sample of children and adolescents and examined the association of rare CNVs with ADHD and OCD traits.
Methods: Quantitative data on ADHD traits using the Strengths and Weaknesses of ADHD and Normal Behavior (SWAN) scale and OC traits using the Toronto Obsessive-Compulsive scale (TOCS) was collected from 17,263 youth (ages 6-17 years) from the community. We genotyped unrelated Caucasians (n=5,366) and East Asians (n=989) using Illumina HumanCoreExome beadchips. CNV were called using three algorithms: iPattern (ipn), PennCNV (pcnv), and QuantiSNP (qsnp) and a high confidence dataset was generated by retaining variants detected by two or more algorithms and at least 10kb in size. We defined rare variants as those with less than 0.1% frequency against our population controls. We plan to examine whether CNV burden, overall and within psychiatrically relevant gene sets (e.g., brain expression, brain development), is associated with ADHD and OCD traits. We will also test if individual CNVs are associated with ADHD and OCD traits.
Results: After stringent quality control, 4857 (90.5%) Caucasian and 933 (94.3%) East Asian samples remained. Total number of CNVs was 31,798 with a mean size of 117,316 base pairs and a maximum size of 7.1 MB. The average number of CNVs per participants was 6. We uncovered 9,836 rare variants, of which 4,151 are deletions and 5,687 are duplications. This comprises of 7,613 rare CNVs from European subjects (mean size = 139,856 kb) and 2,225 from Asian individuals (mean size =123,141 kb). This represented a mean of 1.57 and 2.38 rare CNVs per individuals, respectively. We identified a total of 15 different known genomic disorders from 41 subjects (0.7%) in this cohort. Quantitative trait results forthcoming.
Discussion: Our novel approach will help elucidate the rate of psychiatrically relevant CNVs in the general population and the association of these CNVs with ADHD and OCD. Our preliminary data shows the feasibility of CNV analysis and quality of CNV data from the HumanCoreExome array in a large population based sample.

Disclosure

Ehave - Consultant, Self,
Ironshore Pharmaceuticals - Scientific Advisory Board, Self

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PARENTAL AGE AND DIFFERENTIAL RISK FOR ASD, ADHD, OCD AND TIC DISORDERS: DATA FROM A LARGE NATIONAL COHORT

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Background: Parental age is known to contribute to risk for various neurodevelopmental disorders, including autism spectrum disorder (ASD), schizophrenia, and intellectual disability. In this study we used a population-based cohort to assess the role of parental age in risk across childhood- and adolescent- onset neuropsychiatric disorders including ASD, attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD) and Tourette syndrome/chronic tic disorder (TS/CT).
Methods: Our study cohort included all singleton births, with age data on both parents (n=1,490,745), in Denmark between 1980 and 2007, followed through December 31, 2013. Cases of ASD, ADHD, OCD and TS/CT were identified in the Danish Psychiatric Central Register and the National Patient Register. Both the ADHD and ASD samples overlapped with those in recent reports, while the OCD and TS/CT samples had not been analyzed previously. Associations with parental age were modeled by a cubic spline with 4 knots in stratified Cox regression in which each birth year has its own baseline diagnostic rate while adjusting for the age of the opposite parent.
Results: Cases identified included 16,083 individuals diagnosed with ASD, 25,307 diagnosed with ADHD, 5,324 diagnosed with OCD and 4,666 individuals diagnosed with TS/CT. Younger maternal age was significantly associated with increased risk for ADHD (>1.4-fold increased risk, comparing point estimates of 25 yo mothers to the reference of 30 yo mothers), as well as with increased risk for ASD and for TS/CT. Moreover, association between maternal age and ASD risk followed a U-shaped curve, with increased risk associated with both younger and older mothers. Younger paternal age was also associated with significantly increased risk for ADHD. Advanced paternal age was associated with significantly increased risk for ASD (>1.2 fold at 40 yo), as well as ADHD.
Discussion: Parental age confers differential risk for different child- and adolescent- onset psychiatric disorders and the findings suggest a role for specific, known mechanisms in some of the disorders. Findings of advanced paternal age and risk for ASD and ADHD suggest a role for (1) de novo mutations and/or (2) epigenetic changes in both disorders. The association of younger maternal age with ASD, ADHD and TS/CT suggest that (3) maternal behaviors association with earlier parenting and/or (4) genetic factors that lead to both increased risk for these disorders and younger ages for child bearing are a part of the risk architecture for these disorders. Our results are consistent with a model of distinct and overlapping risk architecture for child- and adolescent-onset neuropsychiatric disease.

Disclosure

Nothing to Disclose.

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GWAS META-ANALYSIS REVEALS NOVEL LOCI AND GENETIC CORRELATES FOR GENERAL COGNITIVE FUNCTION: A REPORT FROM THE COGENT CONSORTIUM

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Background: The complex nature of the human cognitive phenotype has resulted in cognitive genomics lagging behind many other fields in terms of gene discovery using genome-wide association study (GWAS) methods. There were two major aims of the current study: (1) conduct a large-scale GWAS meta-analysis of general cognitive function in 24 independent cohorts (N=35,298), to identify SNP-based and gene-based loci associated with cognition; and (2) determine the extent of genetic correlation between general cognitive function and published neurobehavioral phenotypes of interest. These aims were executed within the context of the Cognitive Genomics Consortium (COGENT), an international collaborative effort designed to study the molecular genetics of cognitive function.
Methods: To date, COGENT has acquired individual-level neuropsychological, demographic, clinical and SNP array data from 24 studies (comprised of 35 sub-cohorts) with 35,298 individuals (46.8% females, mean age of 45.3±8.6 years) of European ancestry drawn from the general population. Genotype data underwent common QC and imputation procedures, resulting in ~8M high-quality SNPs. The GWAS phenotype was general cognitive function ("g"), derived from the first principal component of a PCA performed on an average of 8±4 neuropsychological tests. Allelic association analysis was conducted with imputed allele dosages using Plink 1.9, except for 8 sub-cohorts including related individuals, which were analyzed with BOLT-LMM. GWAS results were combined for meta-analysis using the inverse-variance weighted Z-score method in METAL, with subsequebt gene-based analysis using MAGMA Additionally, we utilized individual SNP lookups and polygenic score analyses (using the LD score regression method) to identify genetic overlap with other relevant neurobehavioral phenotypes.
Results: Our primary GWAS meta-analysis identified two novel SNP loci associated with cognitive performance at the genomewide significance level (P<5E-8). On chromosome 2, intronic SNP rs76114856 in the CENPO gene was genome-wide significant (P=6.58E-9). On chromosome 1, a cluster of six SNPs located in a lincRNA, RP4-665J23.1, were also genome-wide significant (top SNP, rs6669072, P=2.77E-8). In addition, a large 1.4Mb region at chromosome 17q21.31, coextensive with a known inversion polymorphism, harbored 101 nearly-significant SNPs (top SNP, rs916888, P=8.18E-8). Gene-based analysis, as well as integration with prior GWAS studies of cognitive performance and educational attainment (CHARGE, UK Biobank, and SSGAC) yielded several additional significant loci. Finally, we found robust polygenic correlations between cognitive performance and educational attainment, several psychiatric disorders, smoking behavior, and a novel genetic association with the personality trait of openness.
Discussion: These data provide new insight into the genetics of neurocognitive function that are applicable to genetic research of neuropsychiatric illness. Novel genes implicated include CENPO, TP53, ATXN7L2, ARPP21, and RPL31P12. Our results also support several loci derived from the recent CHARGE meta-analysis of general cognitive function, the UK Biobank GWAS of verbal-numerical reasoning, and the SSGAC analysis of educational attainment. Polygenic overlap analyses demonstrate the significance of understanding the genetics of general cognitive function to unraveling the etiology of numerous psychiatric illness and health-relevant conditions.

Disclosure

Nothing to Disclose.

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DISENTANGLING THE SHARED GENETIC ETIOLOGY BETWEEN SERUM CHOLESTEROL AND SUICIDE RISK: A POTENTIAL MODERATING ROLE FOR CHOLESTEROL EFFLUX

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Background: The link between serum cholesterol and suicide attempts is well established, several studies suggest that lower levels of cholesterol are associated with increased risk of mortality from suicide. However, the etiology of this association remains unknown. We present the first study to directly address whether the shared etiology is due to genetic factors.

Methods: All genetic analyses were conducted in SOLAR in a sample of 552 Mexican American individuals from extended pedigrees. The standardized genetic covariances between 23 lipid classes, acquired from 10 μl of plasma, and attempted suicide were calculated. The suicide phenotype was taken from the Suicidality section of the Mini International Neuropsychiatric Interview (MINI). In addition, plasma-based cholesterol efflux capacity (CEC; total, non-ABCA1, and ABCA1-specific) and Lecithin:cholesterol acyltransferase (LCAT) levels were available for all participants. Multilevel mediation analyses were conducted in R using the lme4 and lmerTest packages, this allows the clustering due to family structure to be taken into account.
Results: Both free cholesterol (β = -0.70, p = 2.9x10-04) and lyso-phosphatidylcholine (β = -0.65, p = 2.0-03) exhibited significant genetic overlap with attempted suicide after the application of a multiple comparison correction. Given that the movement of free cholesterol and lyso-phosphatidylcholine have established interactions in the glycerophospholipid metabolism pathway via efflux and LCAT respectively, we investigated these potential relationships in the data. Neither free cholesterol nor lyso-phosphatidylcholine showed an association with LCAT, and lyso-phosphatidylcholine did not show an association with CEC. However, there was a large and significant genetic correlation between free cholesterol and ABCA1-specific CEC (rhog = 0.64, p = 1.38x10-06). Mediation analysis indicated that the relationship between free cholesterol and attempted suicide was significantly mediated by ABCA1-specific CEC (β = 0.07, p = 0.035).
Discussion: While alterations in cholesterol levels have been previously associated with attempted suicide the present study is the first to demonstrate a shared genetic etiology between these two phenotypes. Moreover the results of this study imply that cholesterol efflux, an initial step in the process of reverse cholesterol transport, may be key to the association between free cholesterol and attempted suicide.

Disclosure

Nothing to Disclose.

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THE INTERNATIONAL CANNABIS CONSORTIUM: WHAT DID WE LEARN ABOUT THE GENETICS OF CANNABIS USE

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Background: Cannabis is the most frequently used and abused illicit drug worldwide and cannabis (ab)use is associated with social, physical, and psychological problems. Twin and family studies have shown that cannabis use and abuse are heritable traits. The International Cannabis Consortium was initiated with the aim of identifying genetic risk variants for cannabis use phenotypes by meta-analysing data from many contributing cohorts. The (partly preliminary) results of the International Cannabis Consortium will be presented: genome-wide association (GWA) meta-analyses on lifetime cannabis use and age at initiation of use. Additionally, findings from several follow-up studies will be presented, including the genetic association of cannabis use with use of other substances, schizophrenia, and conduct disorder.
Methods: GWA analyses of lifetime cannabis use were performed by each contributing group independently (13 groups, total N=32,330) and were subsequently meta-analysed. We tested for replication, and the SNP results were used to perform a gene-based test of association. We also estimated the total SNP-based heritability and the genetic correlation between lifetime cannabis use and cigarette use based on LD-score regression analysis. Secondly, we meta-analysed GWA results of age at initiation of cannabis use from 8 groups (N=24,222) using a survival analysis. Again SNP results are followed up by a gene-based test of association and an estimate of SNP-based heritability. In follow-up projects, LD-score regression analyses were used to determine the genetic correlation of cannabis use with nicotine, alcohol, and caffeine use, as well as schizophrenia and conduct disorder. We also created polygenic risk scores for cannabis use in an independent target sample and determined to what extent these polygenic scores predicted conduct symptoms.
Results: Although none of the SNPs were significantly associated with lifetime cannabis use, the gene-based analysis identified 4 significantly associated genes, including NCAM1, CADM2, SCOC and KCNT2. Interestingly, NCAM1 was previously reported to be associated with nicotine and other substance use. All SNPs combined explained 20% of the liability of lifetime cannabis use. For age at initiation of cannabis use, we identified five SNPs (in high linkage-

disequilibrium) that were genome-wide significant. Results of the gene-based test and SNP-based heritability are not available yet. Follow-up studies show a significant genetic correlation of cannabis use with smoking initiation, alcohol use per week, as well as with schizophrenia. Furthermore, polygenic risk scores for cannabis use were significantly associated with symptoms of conduct disorder.
Discussion: The findings of the two largest meta-analyses of GWA studies of cannabis use phenotypes are presented. Several interesting genetic loci were identified, revealing important new candidate genes for cannabis use. Future functional studies should explore the impact of the identified genes on the biological mechanisms of cannabis use. We also show that genes underlying cannabis use are in part overlapping with genes underlying use of other substances and mental health phenotypes, including nicotine and alcohol use, schizophrenia, and symptoms of conduct disorder.

Disclosure

Nothing to Disclose.

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GENETICS OF AGRANULOCYTOSIS UNDER CLOZAPINE

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Background: One major drawback of the therapy with psychopharmacologic agents is the lack of efficacy in many of the patients and the occurrence of side effects that can both limit therapy and compliance. Thus, the availability of a predictive tool for the response to psychopharmacologic agents in the therapy of psychiatric disorders is desirable opening a unique avenue for a real personalized psychiatry. In recent years it became obvious that genetic factors play a substantial role in antipsychotic drug responses and the incidence of side effects. The identification of genetic variants in genes contributing to response variability is the major goal of pharmacogenetic strategies.
Methods: Dan Rujescu will give a talk about the so far largest genome wide association study on agranulocytosis under Clozapine. This study was done within the FP6-EU programme "CRESTAR".
Results: These results are based on several hundreds of patients and several thousand controls. Genome wide association studies as well as sequencing studies were performed. Detected genes will be discussed in the pharmacological context.
Discussion: In summary, this talk should inform the audience about the newest discoveries in pharmacogenetics of agranulocytosis in psychiatry and the transfer to clinical questions.

Disclosure

Nothing to Disclose.

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