with significant mental health issues can successfully maintain their residence in the community which results in significant cost savings, even taking into account the standard MFP costs plus the intervention. MFP Pilot participants improved their functional status, which extended after the intervention period ended. Current implementation efforts are in place to integrate and sustain CAT in the statewide managed care system.

19.3 APPLYING COGNITIVE ADAPTATION TRAINING IN FINLAND: INTERIM RESULTS OF THE FINNISH CAT IMPLEMENTATION PROJECT

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Background: In Finland, approximately 50,000 people have a diagnosis of schizophrenia. In practice 6% of them reside permanently in mental hospitals. There is a national target to reduce the number of psychiatric hospital beds. However, as hospitals are closed there is a tendency to place schizophrenia patients in different types of sheltered housing instead of supporting them to live independently in the community. In the Danish OPUS-study 94 patients with first episode schizophrenia were followed and even those who had attended a vigorous rehabilitation program lived about two and a half months in sheltered housing in the fifth year after their diagnosis. Thus, with deinstitutionalization we are building up a poorly monitored system of sheltered housing for schizophrenia patients. This system may increase chronic need for support, is expensive and marginalizes a large section of people from the community. When service users are asked they usually prefer having their own homes.

Cognitive adaptation training (CAT) is a home-based, manual-driven treatment that utilizes environmental supports and compensatory strategies to bypass cognitive deficits and improve target behaviors and functional outcomes in individuals with schizophrenia. Unlike traditional case management, CAT provides environmental supports and compensatory strategies tailored to meet the behavioral style and neurocognitive deficits of each individual patient. CAT has been shown to be effective in improving service users’ ability live independently.

Methods: The study started in 2014. After formal CAT training the program was implemented in the Hyvinkää Hospital and Helsinki University Central Hospital treatment catchment areas (approx. 1,350,000 inhabitants). For the study we selected patients that were in risk of moving to a more supported housing environment due to the presence of cognitive deficits that threatened their ability to live independently. The only exclusion criteria were heavy alcohol and drug abuse and known aggressive behavior. The outcome measurements include both qualitative and quantitative methods: transfer to a different type of housing, need for hospital treatment, psychiatric rating scales, observed measurements and open interviews, and are measured after 4 months after the start of the intervention, at the end of the 9 month intervention and after a 6 months follow-up period.

Results: We report here preliminary interim results for the patients who have completed the study so far. Altogether 48 patients were selected for the intervention, which was found to be well-received with 7 patients dropping out. The mean age was 38.9 year, with 39.3% women and 60.7% men. 27.6% were living independently, 22.9% with their parents, and 29.6% living in some form of sheltered housing. Participants had severe to moderately-severe psychiatric symptoms and functional impairment (mean GAF 47.8, mean SOFAS 54.8). Apathetic was the most common behavioral subtype (70.7%), with disinhibited (14.6%) and mixed (14.6%) subtypes following.

Discussion: Cognitive Adaptation Training can be used to help patients in a wide range of living situations and with severe psychiatric symptoms and functional impairment to maintain their ability to live independently.

19.4 CAT IN FIRST-EPIODE PSYCHOSIS: FEASIBILITY, ACCEPTABILITY AND POTENTIAL TO ENHANCE VOCATIONAL RECOVERY

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Background: Cognitive and functioning impairments are present early in the course of psychotic disorder and remain one of the greatest treatment challenges in this population. While Cognitive Adaptation Training (CAT) is found to improve a range of outcomes in chronic schizophrenia, it has received limited investigation in first-episode psychosis (FEP). CAT may be particularly useful for addressing vocational recovery in FEP because the cognitive impairments experienced by individuals with FEP predict poorer vocational outcomes and impede the effectiveness of vocational interventions such as supported employment. The aim of this presentation is to present the findings of a pilot study investigating the feasibility and acceptability of CAT in young people with FEP and to describe the clinical considerations and adaptations required when delivering CAT with this population. Preliminary findings on the potential value of CAT in improving vocational outcomes in FEP will also be presented.

Methods: This was a single-arm feasibility study of CAT conducted at the Early Psychosis Prevention and Intervention Centre (EPPIC), Melbourne, Australia. Five FEP participants received 9 months of manually-guided CAT. A range of feasibility and acceptability measures were recorded, including participant and case manager satisfaction ratings. Participants’ goals, functional needs and clinical observations and adaptations were also recorded. Formal measures of functioning, quality of life and motivation were independently administered pre- and post-intervention.

Results: All participants completed the CAT intervention and session attendance rates were very high (95.3%). Participants and their case managers indicated strong satisfaction with CAT as indicated by overall positive mean ratings on the satisfaction items. CAT did not negatively affect existing case management, with case managers reporting that it enhanced their treatment. Vocational recovery (education, employment) was found to be a primary functional goal of most participants. Accordingly, the CAT intervention had a strong focus on vocational functioning, including functional domains that are requisite for successful work or educational outcomes, including organisation and planning, transportation and activities of daily living. Being mindful of factors that may be common in young FEP patients included cognitive heterogeneity, family involvement, flexibility in compensatory and environmental supports used, and the experience of stigma. There were mean improvements from baseline to post-intervention on most formal outcome measures, with the largest effects in global functioning, planning and organisation, and quality of life.

Discussion: This study provides encouraging preliminary evidence that CAT is a highly feasible and acceptable intervention in FEP, which may be easily integrated within existing early intervention services. Vocational recovery is important to young people with FEP. CAT is an intervention that appears well suited to addressing this need. The effectiveness of CAT in improving functional outcomes, particularly vocational recovery in FEP warrants further investigation in a larger trial.

20. THE APPLICATION OF STEM CELL MODELS TO VALIDATE RARE AND COMMON VARIANTS CONTRIBUTING TO SCHIZOPHRENIA

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Overall Abstract: As expanding genetic studies increasingly demonstrate that both rare variants of large impact and common variants of small effect contribute to schizophrenia, it becomes increasingly critical...
that we unravel how these risk factors interact within and between the diverse cell types populating the brain. While mouse models are uniquely suited for demonstrating how aberrant function of single gene products contribute to aberrant neuronal function or behavior, genetic studies of penetrance and complex gene interactions are nearly impossible to address using inbred mouse lines. Similarly, the lack of human post-mortem tissue, coupled with the inability to conduct functional experiments in patient cells, has to date left us with a very limited understanding of how rare and common variants impact gene expression or cellular function. Our panelists have each developed human induced pluripotent stem cell (hiPSC)-based models for the study of predisposition to neuropsychiatric disease, establishing a new mechanism by which to systematically explore the impact of rare and common putative causal variants in human cells.

Given the heterogeneity of schizophrenia and the limited cohort sizes feasible with hiPSC-based cohorts, our panelists will share their successes and struggles in developing cohorts defined by shared clinical or genetic features. They will discuss both the molecular and phenotypic insights they have uncovered, in neurons and glia, from case/control and genetically-edited isogenic cohorts. Our discussant will focus on integrating these findings into consortia-led datasets generated from recent genomic and post-mortem studies of large schizophrenia cohorts. Our overall objective is to consider the role of hiPSC-based studies in dissecting the genetic origins of schizophrenia, validating causal variants identified through ongoing genetic analyses, and serving as a personalized medicine approach to screen for novel therapeutics with which to prevent or reverse disease course.

20.1 DISSECTING THE FUNCTIONAL CONSEQUENCES OF RECIPROCAL GENOMIC DISORDERS

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Background: Reciprocal genomic disorders (RGDs) represent a unique class of recurrent genomic variation that offer insight into highly dosage sensitive regions of the morbid human genome. However, the genomic architecture mediating RGDs, namely non-allelic homologous recombination (NAHR) of flanking segmental duplications, has rendered these genomic segments recalcitrant to conventional model studies. We recently developed a novel CRISPR method that leverages the homology of segmental duplications and efficiently generates large microdeletions and microduplications that mimic NAHR in humans, including ablation or duplication of one copy equivalent of the segmental duplications. Here, we explore the functional consequences of 16p11.2 RGD in iPS derived neuronal models and across mouse tissues.

Methods: We generated CRISPR-engineered 16p11.2 RGD models against an isogenic iPSC background and performed transcriptome profiling in iPSC-derived neural stem cells (NSCs) and induced neurons (iN) (n = 10 isogenic deletions, 10 duplications, 6 controls). We then integrated these data with RNAseq from 306 libraries from multiple tissues in 70 mouse models of reciprocal deletion and duplication of the syntenic 7q13 region (cortex, striatum, cerebellum, liver, white fat, brown fat in 16 mice; and replication from cortex, striatum, cerebellum in 54 mice).

Results: In ongoing analyses, weighted-gene correlation network analysis (WGCNA) identified co-expression modules that were significantly enriched for 16p11.2 genes, evolutionarily constrained genes, genes robustly associated with autism spectrum disorder (ASD; TADA q < 0.1) and developmental disorders (DDD). Pathway analyses within modules discovered enrichment of genes critical to synaptic formation and neural connectivity as well as the protocadherin gene family. Network analyses specific to brain tissues within models further identified a convergence on highly connected, or ‘hub’ genes, on Wnt signaling, including Ctnnb1 and Ctnnd1. The module was also again enriched for ASD loci (TADA, FDR < 0.1), constrained genes (ExAC, pLI ≥ 0.9) and brain specific genes from the Human Protein Atlas.

Discussion: These studies suggest the functional consequences of 16p11.2 RGD across models converge on transcriptional signatures associated with critical neurodevelopmental pathways and individual genes implicated in a spectrum of developmental and neuropsychiatric disorders.

20.2 ANALYZING THE MOLECULAR EFFECTS OF LARGE NEUROPSYCHIATRIC CNVS WITH IPSC BASED NEURONAL TISSUE CULTURE MODELS

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Background: Several large copy number variants (CNVs) in the genomic sequence are strongly associated with schizophrenia. These loci are important objects of study in their own right as well as enticing points of entry for the better understanding of the molecular etiology of schizophrenia. However, most of the schizophrenia-associated large CNVs are larger than one million base pairs and affect up to several dozen genes, presenting a complex challenge for research aiming to determine how these sequence variants are connected on the molecular level to the phenotype.

Methods: We have established iPSC based tissue culture models for three of the major schizophrenia associated large CNVs, on chromosomes 22q11 (deletion), 15q13 (deletion) and 16p11 (deletion or duplication). We create neuronal cells with the defined genotypes using either direct induction into the neuronal state (induced neurons, iNs), by slower differentiation via neuronal precursor cells (NPCs) or by generating 3D cultures of cortical spheroids. We then assay the molecular effects of the large CNVs along the trajectory of differentiation by using RNA-Seq (transcriptome), ATAC-Seq (chromatin state) and SeqCap-Epi (DNA-methylation patterns). We also carry out single-cell RNA-Seq analysis using the drop-Seq approach.

Results: We detect common effects across the large CNVs as well as locus-specific phenomena. For the most part genes within the CNV boundaries will change their expression patterns in concordance with their new copy number, with notable exceptions. Transcriptome-wide there is a network effect where several hundred genes are differentially expressed, including genes already identified as candidate genes for schizophrenia. Epigenomic states are affected, again most often not only in or nearby the boundaries of the large CNVs but epigenome-wide. Integrative analysis across the layers of molecular signals shows partial concordance as well as a degree of changes in signal being ‘offset’ between the levels, potentially owing to the dynamic differentiation state of the model system.

Discussion: Neuronal tissue culture models based on iPSCs with defined large CNVs strongly associated with Schizophrenia allow for an analysis of the effects of such structural genomic sequence changes in disease-relevant cellular differentiation states. Application of cutting edge genomics and epigenomics assays and integrative data analysis reveals incomplete transcriptional dosage compensation of the genes within the large CNVs as well as transcriptome-wide network effects. Furthermore, there are epigenomic effects in the form of altered chromatin states that may to some extent mediate the gene expression changes. Differences between the large CNV loci as well as potential points of convergence will be discussed.