CENTRE FOR INTEGRATIVE SEQUENCING

*i*SEQ lunch seminar series

Talk:
Large-scale DNA and RNA sequencing of schizophrenia cases and controls to reveal associated gene pathways and networks.

Speaker:
Ass. Professor Menachem Fromer, Mount Sinai School of Medicine, New York.

Venue: William Scharff Auditory, The Lakeside Theatres

Time: 4 February 2015 at 12.00 – 13.00

Abstract:
Although schizophrenia is a highly heritable and burdensome psychiatric disease, the exact genes, genetic variants, and pathways involved are still mostly unknown. In this talk, I will discuss how we increased the signal-to-noise ratio in our two next-generation DNA sequencing studies of schizophrenia. In one, ~2500 schizophrenia cases and ~2500 matched controls were whole-exome-sequenced. The magnitude of neutral mutations largely overwhelms the number of genetic variants more likely related to disease, which we focus on by frequency filtering, biological impact, and pathway analysis. In the second study, de novo mutations were sought out in father-mother-child trios to find mutations not yet subjected to selective pressures. In this instance, the overwhelming majority of such potential mutations (seemingly arising as new in the children) are false positives. We carefully sifted through these using sequencing and other metrics to find the real ones most likely associated with disease. In the literature, analyses of protein-protein interaction (PPI) networks have been successfully used to interpret results from genome-wide association studies (GWAS), copy number variant (CNV) and sequencing studies, using tools such as DAPPLE. Such approaches test whether associated genes code proteins that interact (are connected in a PPI network) more than expected by chance. Greater connectivity adds orthogonal support for the associations, can be used to prioritize specific genes, suggest new candidates, and potentially provide insights into the underlying biology. Thus, our follow-up work has expanded on these PPI approaches to comprehensively enable testing for enrichment of overall connectivity ("hub proteins"), direct connectivity between associated genes, indirect connectivity among associated genes, and comparisons and contrasts of two sets of genes for their shared and differential connectivities. Further, as an alternative to controlling for overall protein connectivity, our permutation framework can control for gene size, mutation rate, and sequencing coverage of the exome. We have applied this framework to a number of recent datasets of de novo mutations, primarily in

neuropsychiatric disease, including autism, intellectual disability, schizophrenia, and epilepsy. The most recent schizophrenia GWAS (summer 2014) reported >100 associated loci, implying a high degree of polygenicity. To better understand the pathology of neuropsychiatric disease, we have formed the CommonMind Consortium (commonmind.org) to generate large-scale functional genomic data (RNA-seq, ChIP-seq, DNA-seq/genotyping) from human post-mortem brain samples. Here, we identify changes in gene expression using RNA-seq of ~600 samples from the dorsolateral prefrontal cortex (BA9/46). Clinical (gender, age of death, medications) and technical (brain bank, post-mortem interval, RNA quality, sequencing batch) covariates, as well as hidden confounders, were controlled using surrogate variable analysis (SVA). Application of linear models implemented in voom/limma identified ~500 of expressed genes as differential between cases and controls. These genes were nominally enriched for DNA variants associated with schizophrenia, including common GWAS loci. De novo loss-of-function (nonsense, frameshift, essential splice site) mutations in schizophrenia and epilepsy affected the differential genes, though this did not hold for autism or intellectual disability de novos (nor for unaffected controls). Gene coexpression networks constructed using WGCNA (Weighted Gene Co-expression Network Analysis) identified ~25 modules, some differentially expressed. This large dataset will be made public in early 2015.

Refreshments:

Sandwiches will be provided. Therefore, please email Anne Hedemand (anne@biomed.au.dk) no later than 3 February 2015, if you would like to participate.