Brunilda Balliu talks about statistical methods for contextualization of genetic associations using multi-context functional genomic data. eQTL, expression quantiative trait loci, mapping can provide key insights into the function of disease-associated variants as it can connect disease-associated non-coding variants to the genes they affect. However, large-scale eQTL studies have demonstrated extensive sharing of eQTLs and this complicates the identification of disease-relevant contexts. To understand these contexts, studies often use repeated sampling from the donors and use certain approaches for analysis. The intra-individual residual correlation approach is fast, but is significantly underpowered as it reduces power to detect context-specific eQTLs. To resolve this problem, another approach, FastGxG, a novel method that leverages the correlation structure to effectively map context-specific eQTLs. FastGxG decomposes the phenotype of interest per individual into context-specific and context-shared components and estimates the genetic effects. The decomposition looks like this, The FastGxG is able to identify widespread pleiotropy and specificity of eQTLs across tissues in GTEx. And it also increases precision to identify disease-relevant tissues for cancer traits. Another study that Brunilda talked about was CONTENT, an approach to link genes with complex traits using cross-context TWAS. It turns out that this approach outperforms existing approaches in GTEx as it predicts the expression of more genes with higher accuracy and increases number of gene-trait associations. As Brunilda’s future work, she will be moving from bulk tissues to single cell profiling because the specific cell typed eQTLs can better help us understand disease loci that are not explained by eQLTs in bulk tissues. The shift also includes moving from static QTLs to dynamics as it can explain disease loci that are not explained by static eQTLs.

Eirene talks about the chromatin regulation in cortical development and autism. She first introduced the importance of mid-fetal development for neurogenesis and psychiatric illness and indicates the puzzling difficulty of autism spectrum disorder, which is the social communication impairment and repetitive behaviors. In order to study the genetic variants that regulates enhancers that causes autism, she mapped open chromatin regions in the 14-22 week sample fetal brain and isolated the nuclei and access genome-wide chromatin using a ATAC-seq as the sequencing assays. After identifying regional and layered enhancers and integrating entire genome sequencing data from autism patients, Slc6a1 was compared and thought to be a high confidence autism spectrum disorder gene and also associated with epilepsy/absence seizures with developmental delay. One challenge was the studying of transcriptional regulators of enhancers. Another risk factor gene, POGZ gene was studied. Beyond its ability to bind DNA, there is little knowledge about POGZ’s transcription or chromatin state. To further investigate, Eirene generated a knockout mouse and dissected chromatin state phenotypes of mouse. Again, isolating nuclei and underwent the ATAC-seq. And her analysis revealed POGZ enhancer binding promotes transcription of neuronal genes and forms the protein HP1y and ADNP, another autism spectrum risk gene. Eirene’s further research will interrogate POGZ’s transposase domain which she will study to how POGZ alter how tightly regions of DNA are packaged.