# Deciphering the molecular basis of neuronal development deficits in the recurrent genomic disorder

**Derek JC Tai**
Center for Genomic, USA

Reciprocal copy number variant (CNV) of chromosomes 16p11.2 (OMIM 611913), 15q13.3 (OMIM 612001), and 15q11.2-13.3 [Prader-Willi syndrome (PWS), OMIM 176270] are the highly significant recurrent genomic disorders (RGDs) associated with intellectual disability and autism spectrum disorder. The non-allelic homologous recombination (NAHR)-mediated CNV results from mispairing of the flanking segmental duplications, which can result in either loss or gain of the unique genic segment (600 kb in 16p11.2 RGD; 1.5 Mb in 15q13.3 RGD; 5.3 Mb in PWS RGD). However, the pathogenic mechanism and the functional relevance of individual genes within RGDs and the combined contributions of multiple genes are not known. To interrogate the region against an isogenic background, we developed a novel CRISPR/Cas9 genome engineering approach to efficiently generate reciprocal CNV that mimics NAHR. With the comprehensive cell models and the integrated molecular and computational approaches, we attempt to uncover the molecular basis for abnormal neurodevelopment in these disorders by recapitulating neuropathology of RGD in derivative neuron models. Our preliminary data and several recent studies have strongly suggested KCTD13 and CHRNA7 might be one of the drivers of 16p11.2 and 15q13.3 RGDs respectively. We then defined cellular phenotypes, transcriptional signatures, and co-expression modules that are differentially altered by RGDs. Our transcriptome profiling and analyses showed that genes regulating cytoskeleton (GO:0005856) and translational initiation (GO:0006413) were significantly altered in the neurons with 16p11.2 CNV, and the genes involving axon guidance (GO:0007411) and Wnt signaling pathway (KEGG:04310) aberrantly expressed due to 15q13.3 perturbation. The neuron phenotyping experiments revealed aberrant neurite length, branch points, and electrophysiological features in the RGD neuron models. These studies will allow us to gain more insights into the relationship of gene expression to phenotype and the pathogenic mechanism underlying the disease.

**e**: jctai@mgh.harvard.edu