

The Future of Genomics - Impact on 22q11.2DS and Vice Versa

One of the most pressing challenges facing clinical genetics and genetic counselling is the high degree of variable expression of pathogenic variants. This is particularly well appreciated for recurrent copy number variants (CNVs) such as 22q11.2 deletion syndrome (22q11.2DS) where many genes influence phenotypic expression. The 22q11.2 deletion displays 100% penetrance globally; however, penetrance for individual associated features is incomplete, whether one considers those of early onset like congenital cardiac and/or palatal anomalies, or of later onset like schizophrenia (which affects 1 in 4 patients). A substantial proportion of this variability is likely conferred by additional genetic factors located elsewhere in the genome and it is crucial to delineate the contribution of these variants in order to effectively aid in diagnosis and personalize risk prediction for patients.

It is well known that both rare and common variation contributes significantly to risk for neurodevelopmental disorders. We hypothesize that both rare and common genome-wide variants will be involved in modifying expression of major phenotypes in 22q11.2DS. Until recently it has been difficult to fully test this hypothesis due to technical limitations and/or prohibitively high cost but recent sequencing advances have made it feasible to interrogate the genome at unprecedented resolution. Whole genome sequencing (WGS) represents a comprehensive platform for detection of rare and common sequence and structural variation (SV) in a single experiment and identify primary diagnostic variants and important modifiers of expression in a single experiment.

The International 22q11.2 Brain Behavior Consortium (IBBC) has amassed phenotypic and WGS data for ~1500 individuals, all of whom have a confirmed 22q11.2 deletion. This valuable dataset provides a unique opportunity to examine the penetrance of major associated features and the variable expression and severity of the many possible associated features. We have initial evidence that rare genetic variants that are additional to the 22q11.2 deletion act as modifiers of expression of schizophrenia and of congenital cardiac disease in 22q11.2DS. These include both rare structural variants (e.g., copy number variation, CNV) and sequence-level variants (e.g., single nucleotide variants, SNVs). In addition, we have evidence that background effects of common variants can affect penetrance in 22q11.2DS. Using 22q11.2DS as a model, insights gained from these studies can inform our approaches to other genetic syndromes and the results promise to shed light on the complex genomic architecture of brain diseases across the lifespan in the general population.