**Jan Friedman (Dept of Med Gen, UBC)**

Finding rare genetic disease genes. Clinical genetics perspective.

**Rare**: affecting < 1:2000; together affect ~3% of population, 80% affected in childhood. **rare and characteristic phenotype; little or no genetic heterogeneity**

Difficult to determine **causal** variant (signal vs noise!). Ex. Intellectual disability -> >700 genes (and counting).

Rare diseases get complicated: Episodic and then goes away – disease is not persistent (ex. Dystonia, CAPOS, dementia with epilepsy).

Most families with autosomal dominant disease tend to be small.

Homozygosity vs compound heterozygosity: Both may be potential cause of a rare disease seen in >=2 affected sibs, nonconsangeious.

*Acquisition of a new dominant mutation is a common cause for rare genetic diseases.*

Phenotyoe can be at a different tissue – usually use blood as a representation. 10,000x coverage used nowadays to address this – but we are still testing the wrong tissue, and a variant needs support before it can be called. Current pipelines also cannot identify TNR expansions with exome sequencing (ex. Fragile X syndrome).