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Talk Title: **Cilia in the complex genetics of congenital heart disease**

Abstract:
Congenital heart disease is one of the most common birth defects, affecting up to 1% of newborns. While it is well described to have a strong genetic underpinning, as yet its genetic etiology is still poorly understood. With large scale human exome and whole genome sequencing data becoming readily available, large patient cohorts have been sequenced to investigate the genetic etiology of congenital heart disease. These studies have mostly focused on identifying de novo mutations with large effects, but these can account for only ~10% of congenital heart disease. While a handful of heritable mutations have been identified, the genetic causes of the large majority of congenital heart disease remain unexplained. Genetic studies in patients have been confounded not only by the genetic heterogeneity of the human population, but also the incomplete penetrance and variable expressivity associated with congenital heart disease. To address these limitations, we have undertaken a large scale mouse forward genetic screen in inbred C57BL6/J mice to interrogate the genetic etiology of CHD.

We conducted a large scale screen with inbred C57BL/6J mice using chemical mutagenesis with ENU to introduced random mutations in the genome. A two generation breeding scheme was used to allow for the recovery of recessive mutations. To identify fetuses with congenital heart disease, noninvasive high throughput cardiovascular phenotyping was conducted using fetal echocardiography, a very sensitive imaging modality also used clinically for the diagnosis of congenital heart disease. From screening over 100,000 fetal mice, we recovered over 200 mutant lines with a wide spectrum of congenital heart disease. Using whole exome sequencing analysis, mutations were recovered in over 150 of the mutant lines, identifying mutations in 100 genes. We found two thirds of the genes recovered were cilia related. As the screen was agnostic to genes or pathways, these findings suggested cilia biology plays a central role in the pathogenesis of congenital heart disease. Interestingly, many of the genes recovered are direct protein-protein interactors, suggesting a protein interactome network may comprise the genomic context in which the genetic architecture of congenital heart disease may have emerged.

While this forward genetic screen was conducted to recover recessive mutations, the screen also yielded evidence for multigenic etiology of congenital heart disease. Notable in this regard was the recovery of the first mouse models of hypoplastic left heart syndrome (HLHS). Analysis of 8 mutant lines with HLHS indicated that this congenital heart disease has an obligate multigenic etiology. This explains the previous failure to generate mouse models of HLHS using KO and transgenic mouse approaches. As congenital heart disease in the human population is often observed to be sporadic and associated with dominant mutations, we pursued a sensitized mouse forward genetic screen designed to recover dominant mutations causing congenital heart disease. Surprisingly, we found the incidence of dominant mutations causing congenital heart disease was similar to that observed for recessive mutations in the recessive screen. Moreover, the recovery of dominant mutations causing congenital heart disease from two mutant mouse lines again recovered two cilia related genes, both found within the cilia related protein interactome network identified in the recessive screen. Together these findings suggest the genetic architecture underlying the complex genetics of congenital heart disease may be captured by the interactome network of cilia related genes. Together they may contribute to dominant, recessive, and multigenic model of disease pathogenesis in congenital heart disease.