Genetic mapping of cardiomyocyte ploidy phenotypes that influence basal cardiac physiology

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Identifying genes that contribute to heart failure and variable heart function has proven to be challenging due to high genetic diversity of patient populations, inability to control for non-genetic factors, and cellular-level complexities that contribute to outcomes. Here, we propose utilizing the Hybrid Rat Diversity Panel (HRDP) to assess high throughput surrogate phenotypes, which can be predictive of disease outcomes when measured in the basal state. Our surrogate phenotype of interest is cardiomyocyte (CM) ploidy, where an increased proportion of hyperpolyploid (≥8N) CMs is associated with adverse ventricular remodeling and dilated cardiomyopathy.

Having analyzed 76 of the 96 HRDP strains, I observed that frequency of diploid CMs varied from 1.2-21.8% across strains, while frequency of the hyperpolyploid CMs varied from 0.8-20.7%. To assess whether CM ploidy is associated with cardiac function and gross morphology, 12 strains were selected for further studies. Both CM ploidy phenotypes correlated with left ventricular ejection fraction and left ventricular area, while frequency of hyperpolyploid CMs alone correlated with LV mass. These baseline correlations could indicate that increased CM ploidy results in dilation of the LV with reduced contractility.

Preliminary mapping results from 69 strains resulted in 2 significant loci, as well as 4 suggestive loci for the frequency of hyperpolyploid CMs. Within the locus on Chromosome 14 resides *Shroom3*, a gene that harbors an established damaging variant (G1073S) that is associated with hyperpolyploidy and which has been previously linked to kidney dysfunction but with unknown function in the heart. We have also identified 2 novel, predicted-to-be-damaging variants (G852R and R977W), which are instead are found in strains with high frequencies of diploid CMs. Studies to examine the effect of these variants on protein function and assess their respective ability to rescue adverse cardiac phenotypes observed in a *Shroom3* conditional knockout mouse are currently in progress.