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Discovery of Novel Genes Associated with Congenital Heart Disease

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Mutations of the cardiac transcription factor Nkx2-5 in humans cause congenital heart defects, a leading cause of death in infants. Heterozygous Nkx2-5 mice likewise develop heart defects, but the incidence varies with genetic background. My hypothesis was that these strain-specific differences arise from differences in gene expression in the different strains of mice we observe. The goal of my work was to find alleles linked to Nkx2-5 outside the 10 Mb region upstream of the Nkx2-5 locus on chromosome 17, as alleles in this region are linked to Nkx2-5.

To test this hypothesis, an RNA-Seq experiment was conducted in which RNA was isolated from hearts of 21-day old mice of a variety of genetic backgrounds. The RNA was sent to a core facility for sequencing, and the resulting data was analyzed using a statistical genomics package. Statistical tests such as two-way ANOVA and receiver-operator curves were performed on the known Nkx2-5 linked alleles on chromosome 17 to establish threshold criteria for true positive alleles. Based on these numbers, a list of 50 potential candidate alleles was generated. These alleles were validated using a mass-spectrometry method. Positive controls were the differentially expressed alleles in the 10 Mb region upstream of Nkx2-5 (true positives) and negative controls were equally expressed alleles outside this region (true negatives).

Results from this first set of alleles were inconclusive. Positive and negative controls behaved as expected, but the candidate SNPs were not consistent among the samples. Hearts will be isolated from more mice throughout the semester to assess other SNPs that may be potential candidates for the experiment.