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Zebrafish: A Model to Identify Novel Genetic Causes of Human Heart Disease

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The goal of this dissertation is to use the zebrafish genetic model to identify novel genetic causes of vertebrate cardiovascular dysfunction that will ultimately provide insight to genotype-phenotype correlations and enable the development of new therapeutic and preventive concepts for inheritable human cardiovascular diseases. In order to accomplish this goal three tasks were addressed: (i) assignment of unique chromosomal loci for each of eight zebrafish mutants displaying cardiovascular dysfunction, (ii) phenotypical characterization and fine mapping of three of these mutants: *sisyphus*, *reggae* and *flatline,* and (iii) identification of the gene containing the mutant loci for *reggae* and *flatline*. The forward genetics approach was used to accomplish these tasks. The methods used for the forward genetics approach included initial linkage assessment through Bulk Segregation Analysis, establishing a closed genetic interval by recombination analysis through individual genotyping of polymorphic alleles, sequencing of candidate genes in order to identify point mutations, and knockdown experiments to determine if loss of gene function indeed caused mutant phenotype. We were successful in assigning all eight mutants a unique chromosomal locus and in defining a closed genetic interval. We successfully determined that of *reggae* and *flatline* encoded mutations in *zerg* and *zsmyd1* respectively. Further experimentation led us to the conclusion that *reggae* is the first animal model for human Short QT Syndrome, as the *reggae* mutation in *zerg* has a gain of function. Also, that *smyd1* in zebrafish is a novel regulator of myofibrillogenesis in heart and fast skeletal myocytes.