S6_7

Identifying Mitral Valve Prolapse Mutations on Chromosomes 11 and 13 Using Next-generation Sequencing

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Mitral valve prolapse (MVP) is a common cardiac disorder that exhibits a strong hereditary component. Twenty percent of MVP patients will develop complications, including congestive heart failure, endocarditis, atrial arrhythmias, embolic events and sudden death. Surprisingly, very little is known about the developmental etiology of MVP. Previously, we identified two MVP loci using genetic linkage analysis in large families: MMVP2 on chromosome 11p15.4 and MMVP3 on chromosome 13q31.3-32.1. We were recently awarded an R102 NHLBI Resequencing and Genotyping Service grant that allowed us to capture and sequence these loci. All sequencing was performed at the Venter Institute. A DNA library of the two loci was prepared using SureSelect technology. After excluding repeat elements we targeted ~50% of each locus. Four individuals from each family, who share only the disease allele, were selected for sequencing. Sequencing was performed on the Solexa sequencer. 97% of the targeted area was sequenced and the average coverage was 310X. Single nucleotide polymorphisms (SNPs) were identified and characterized as potential mutations if they were 1) shared by all four individuals in the family and 2) not present in dbSNP or other public databases. After analyzing familial sharing, there were 155 potential mutations on chromosome 11 and 308 on chromosome 13. These potential mutations were prioritized and evaluated in the following order: 1) coding sequence changes, 2) promotor or splice site changes, and 3) changes in evolutionary conserved regions. Using these criteria, we identified several potential missense mutations in the MMVP2 locus. There are no coding changes in the MMVP3 locus, but there are 25 changes in highly conserved regions adjacent to three genes, GPC6, GPC5 and HS6ST3. We are currently evaluating these mutations for potential function and initiating sequencing in a large cohort of familial and sporadic MVP patients in order to identify additional mutations.