Novel Genetic Modifiers of Heart Failure

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Prior targeted association studies have suggested that common genetic variants in ion channels, adrenergic receptors, neurohormonal genes, and calcium handling genes are associated with heart failure progression (pump failure death/ventricular assist device placement/heart transplant) and/or arrhythmias (sudden cardiac death; SCD). Genome wide association studies (GWAS) have been used to identify novel genetic variants in an unbiased manner. Many of the putative associations have not been adequately replicated, and none are currently used in clinical practice.

Subjects with ejection fractions (EFs) ≤0.30 and implantable cardioverter defibrillators (ICDs) were enrolled in the 5-year, prospective, Genetic Risk Assessment of Defibrillator Events study performed at the University of Pittsburgh, the Pittsburgh VA Medical Center, Massachusetts General Hospital, Emory University, Mid Ohio Cardiology and the Ohio State University. Median follow-up on the 1808 subjects was 30.8 months. The cohort was 80% male, 79% white, 20% African American, and 70% ischemic; mean age was 62±12 years, mean EF was 0.21±0.06, and mean NYHA class was 2.2±0.6. Polymorphisms were genotyped by real time PCR or by iPlex. Freedom from appropriate ICD shocks (a surrogate for SCD; the primary endpoint) and survival (a secondary endpoint) were compared by genotypes, alleles and haplotypes using Kaplan-Meier analysis and Cox regression models.

Age, ischemic etiology, EF, and NYHA class predicted survival, while ischemic etiology, EF, and African American race predicted appropriate ICD shocks. LV size was identified as a novel independent predictor of both arrhythmias and survival. Gln27 homozygotes for the β2-adrenergic receptor (*ADRB2*) Gln27Glu single-nucleotide polymorphism (SNP) have previously been shown to have increased risk of SCD, but the effect of *ADRB2* variants in cardiomyopathy patients at high risk for arrhythmias and SCD is unknown. In GRADE, Gln27 homozygotes had more appropriate shocks than Glu27 carriers (log rank P=0.004), which persisted after covariate adjustment in Cox regression models (OR=1.4, CI =1.1-1.7, P=0.009). The Gln27 polymorphism did not predict survival. Alanine allele carriers of the Ser96Ala (S96A) SNP in the histidine-rich Ca2+-binding (HRC) protein, a low affinity sarcoplasmic reticulum (SR) Ca^{2+} buffer, had more ventricular arrhythmias and SCD in a small prior case-control study. In GRADE, carriers of the HRC 96A allele (heterozygotes and homozygotes) experienced significantly more appropriate ICD shocks than SS homozygotes (P=0.04), with no difference in survival.

Thus, polymorphisms in adrenergic receptor and calcium handling genes are associated with increased risk of SCD in heart failure patients. This genetic information may be useful for supplementing clinical information to help to identify a high risk subgroup of heart failure patients that would benefit most from ICD placement.