REGULATION OF PLASMA ET-1 LEVELS BY CHROMOSOME 4Q25 SNP ASSOCIATED WITH ATRIAL FIBRILLATION

ACC Poster Contributions
Georgia World Congress Center, Hall B5
Sunday, March 14, 2010, 9:30 a.m.-10:30 a.m.

Session Title: Genetics and Cardiac Events
Abstract Category: Genetics and Clinical Outcomes
Presentation Number: 1027-154

Authors: Fadia Mayyas, Jonathan D. Smith, John Barnard, Mina K. Chung, David R. Van Wagoner, Cleveland Clinic, Cleveland, OH

Background: A single nucleotide polymorphism (SNP, rs2200733) on chromosome 4q25 is strongly associated with atrial fibrillation (AF). The biological significance of this SNP is unknown, but it is located near and may modulate expression of a transcription factor, PITX2. As a link between PITX2 and endothelin-1 (ET-1) signaling has been suggested, we hypothesized that the 4q25 SNP may modulate ET-1 signaling.

Methods: The rs2200733 SNP was genotyped in a lone AF cohort. To test whether the SNP is correlated with plasma ET-1 levels (pET1), ET-1 was assessed by ELISA (Biomedica BI-20052) in plasma samples from 119 individuals (30 TT, homozygous for the risk allele; 43 CT heterozygous, and 46 CC homozygous for the major allele). Groups were matched for age, gender and hypertension (HT).

Results: Box plots (median, 25th, 75th percentile) show that pET1 levels were higher in lone AF patients homozygous for the risk allele (TT, p<0.0006) than in the CT or CC patients. Data support an additive rather than dominant model. Univariate predictors of pET1 levels also included age and systolic blood pressure (BP), but not diastolic BP or BMI. In a multivariate model, genotype, followed by age, were the strongest and only significant predictors.

Conclusions: The SNP rs2200733 is strongly associated with plasma ET-1 levels in lone AF patients. ET-1 is associated with HT, modulates myocyte calcium cycling, and promotes cardiac hypertrophy and fibrosis. ET-1 may contribute to the increased risk of AF in subjects with this genotype.