RARE CODING MUTATIONS AND RISK FOR EARLY-ONSET MYOCARDIAL INFARCTION: AN EXOME SEQUENCING STUDY OF >2,000 CASES AND CONTROLS

ACC Moderated Poster Contributions
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Myocardial infarction (MI), the leading cause of death in the U.S., is a heritable phenotype and the role for inheritance is greatest when MI occurs early in life. While genome-wide association studies (GWAS) have identified at least 30 common variants associated with MI, the modest proportion of heritability explained suggests that variants low in frequency (1% to 5% frequency) or rare (<1% frequency) may contribute to risk for early-onset MI (EOMI). To test the hypothesis that rare coding mutations contribute to EOMI risk, we are sequencing all protein-coding regions of the genome (the “exome”) of ~1,200 cases with EOMI (men ≤ 50; women ≤ 60) and ~1,200 controls free of MI. Using next-generation sequencing, we have targeted 32.7 megabases at 188,260 exons from 18,560 genes. In the first 970 exomes, we have generated ~6 billion bases of sequence per individual. Each targeted base was read 139 times on average, and for each individual ~88% of bases were covered with at least 20x depth. We performed rare variant burden tests, single SNP association tests, and imputed exomic variants into completed MI GWAS datasets. In burden tests, we find an excess of rare mutations (all non-synonymous with MAF < 1% (T1) or 5% (T5)) in several genes including CHRM5 (P=0.00014 for T1), NBEAL1 (P=0.00015 for T1), and LRIG2 (P=0.0002 for T5). In single SNP association tests, we re-discovered a known nonsense mutation in PCSK9 that confers protection against MI (seen in 0 of 466 cases and 6 of 504 controls). In imputation using EOMI exomes as the reference panel, we re-discovered the association of a known low-frequency missense SNP in LPA (I4399M, 2% frequency, P < 5x10^-8). We are replicating findings from the discovery study using three approaches: (1) Sanger sequencing in independent samples (500 cases and 500 controls) of specific genes with signal based on a burden of rare mutations; (2) genotyping of 212 low-frequency SNPs in >10,000 independent MI cases and controls; and (3) imputation of exomic variants into >35,000 MI cases and controls with GWAS data. These replication results should provide insight into the role of rare variants in conferring MI risk and the role of exome sequencing to understand the inherited basis for complex traits.