Examining genetic susceptibility to anthracycline-related cardiomyopathy in cancer survivors using a gene-level approach

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ABSTRACT

The inter-individual variability in anthracycline-related cardiomyopathy risk among childhood cancer survivors has been attributed to associations with single nucleotide polymorphisms (SNPs). Considering effects of multiple SNPs on a gene and their interactions, however, remains unexamined. We used whole exome sequencing data to examine gene-level associations with cardiomyopathy among survivors of childhood cancer. For discovery, a matched case-control set of 278 childhood cancer survivors (129 cases; 149 controls) from COG-ALTE03N1 utilized logic regression to identify gene-level SNP combinations in 7,212 genes and ordinal logistic regression models to estimate gene-level associations with cardiomyopathy. Models were adjusted for primary cancer diagnosis, age at cancer diagnosis, sex, race/ethnicity, cumulative anthracycline dose, chest radiation, cardiovascular risk factors, and three principal components. Statistical significance threshold of 6.93x10⁻⁶ was used to account for multiple testing. Three independent cancer survivor populations were used to replicate gene-level and assess individual SNP associations: Childhood Cancer Survivor Study (CCSS) and Bone Marrow Survivors Study (BMTSS cohorts and a non-overlapping COG-ALTE03N1 case-control set. Median age at childhood cancer diagnosis for the discovery cases and controls was 6 and 8 years, respectively. Gene-level analysis identified statistically significant associations for PR2X7 (OR=0.10; 95%CI: 0.04-0.27, P=2.19x10⁻⁵), TNIK (OR=4.58; 95%CI: 2.47-8.49, P=1.34x10⁻⁵), LRRK2 (OR=0.19; 95%CI: 0.09-0.39, P=6.62x10⁻⁶), MEFV (OR=0.08; 95%CI: 0.03-0.24, P=4.07x10⁻⁶), NOBOX (OR=7.21; 95%CI: 3.23-16.1, P=1.43x10⁻⁶) and FBN3 (OR=4.59; 95%CI: 2.42-8.71, P=3.05x10⁻⁶). The gene-level SNP combination on P2RX7 was successfully replicated in the CCSS cohort (HR=0.65; 95%CI: 0.47-0.90, P=0.009). Individual SNPs across all significant genes, except FBN3, were associated with cardiomyopathy. In silico functional evidence supported the findings with biologically plausible links to inflammatory responses and cardiovascular disease in non-oncology populations. Specifically, P2RX7 protein antagonism has protective cardiovascular effects lowering blood pressure and atherosclerosis progression. Gene-level associations identified in this study have the potential to identify individuals at increased risk for cardiomyopathy and inform future discovery of therapeutic targets to mitigate this adverse outcome.