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 6.93×10^{-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, $P=2.19 \times 10^{-6}$), *TNIK* (OR=4.58; 95%CI: 2.47-8.49, $P=1.34 \times 10^{-6}$), *LRRK2* (OR=0.19; 95%CI: 0.09-0.39, $P=6.62 \times 10^{-6}$), *MEFV* (OR=0.08; 95%CI: 0.03-0.24, $P=4.07 \times 10^{-6}$), *NOBOX* (OR=7.21; 95%CI: 3.23-16.1, $P=1.43 \times 10^{-6}$) and *FBN3* (OR=4.59; 95%CI: 2.42-8.71, $P=3.05 \times 10^{-6}$). 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.