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Disclaimers:
The views expressed in the submitted abstract are his or her own and not an official position of the institution of funder. There are no conflicts of interest.

Sources of support:
Funding for this project came from the National Cancer Institute [Z01 CP010131-23 (National Institutes of Health Intramural Program), U24 CA55727, U01 CA195547, P30 CA21765 (Cancer
Center Support CORE grant) and R01 CA216354, the Leukemia and Lymphoma Society and the American Lebanese Syrian Associated Charities, Memphis, Tennessee.

**Genome-wide association study using whole-genome sequencing identifies a novel locus associated with increased risk of cardiomyopathy in adult survivors of childhood cancer: utility of a 2-stage analytic approach**

**Background:** Survivors of childhood cancer are at increased risk of treatment-related cardiomyopathy, found to be modified by genetic factors. To further investigate genetic risks of cardiomyopathy, we utilized whole-genome sequencing (WGS) in a clinically phenotyped cohort of long-term survivors of pediatric cancer.

**Methods:** Utilizing a novel 2-stage analytic approach, we first performed association analysis for ejection fraction (EF) using WGS data in European-descent childhood cancer survivors from the St. Jude Lifetime Cohort (SJLIFE). EF was analyzed as a continuous variable to increase statistical power for genetic discovery. Common variants (minor allele frequency (MAF) > 0.05) were analyzed using linear regression, adjusting for age at diagnosis, sex, age at follow-up, doses of anthracycline and average radiation dose to the heart, and eigenvectors. Rare/low-frequency variants were aggregated by different functional annotations and agnostic 4-kb sliding windows, testing jointly using Burden/SKAT test. In the second stage, only the variant showing genome-wide significance with EF was tested for its association with cardiomyopathy risk.

**Results:** Among the 2,015 SJLIFE survivors with WGS data, a locus on 6p21.2 near KCNK17 achieved genome-wide significance with EF (rs2815063; MAF = 0.13; per allele beta = −0.016; \(P = 2.10 \times 10^{-8}\)), which replicated in 320 SJLIFE African survivors (MAF = 0.48; beta = −0.015; \(P = 0.004\)). In SJLIFE Europeans, 282 had a CTCAE Grade 2-5 cardiomyopathy. rs2815063 was significantly associated with increased risk of cardiomyopathy [per allele odds ratio (OR) = 1.38; \(P = 0.02\)], which replicated in 3,957 European survivors from the Childhood Cancer Survivor Study (163 CTCAE Grade 3-5 self-reported cases; per allele OR = 1.39; \(P = 0.038\)). rs2815063 alters DNA binding motif of EWSR1-FLI1, whose expression was found to lead to cardiomyopathy and death due to chronic cardiac failure in mice.

**Conclusions:** Using a 2-stage approach, we report a novel locus for cardiomyopathy in childhood cancer survivors, which warrants additional work to gain mechanistic insights.