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**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; $P = 2.10\times10^{-8}$), 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.