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A genome-wide association study for doxorubicin-induced cardiomyopathy in childhood cancer survivors from the St. Jude Lifetime Cohort (SJLIFE) and the Childhood Cancer Survivor (CCSS) Studies.

Impact Statement

The use of doxorubicin in childhood cancer treatment is recognized to correlate with a dose-dependent susceptibility to cardiomyopathy, which can lead to heart failure and affects ~7-10% of exposed children and adolescents. Leveraging the two largest cohorts with available germline genetic data from childhood cancer survivors in North America, we identified and replicated a novel locus near HS3ST4, specific to doxorubicin-induced cardiomyopathy. This finding could guide further research into the underlying mechanisms of doxorubicin-induced cardiomyopathy, could be instrumental in identifying survivors at risk and pave the way for the development of targeted interventions and novel therapeutic strategies.

Abstract

Background: Treatment of childhood cancer using doxorubicin is associated with a well-established dose-related risk of cardiomyopathy.

Methods: A genome-wide association study was performed among 993 SJL1FE survivors of European ancestry treated with doxorubicin only (210 with cardiomyopathy; defined as CTCAE grade >= 2). Replication analyses were performed separately among 1.430 CCSS survivors of European ancestry and 159 SJLIFE survivors of African ancestry exposed to doxorubicin only.

Results: We identified a genome-wide significant association between a novel locus near HS3ST4 and cardiomyopathy risk in SJLIFE survivors of European ancestry (rs112474856; OR= 2.78; P=3.3x10-8). This association replicated in CCSS survivors of European ancestry (OR=l.74, P=0.036) but had an opposite effect among SJLIFE survivors of African ancestry (OR=0.34,
P=0.028). SNP rs112474856 did not show significant association with cardiomyopathy risk in two independent datasets including survivors of European ancestry in SJLIFE (OR=l.20; P=0.71) and CCSS (OR=l.02; P=0.98) who were not exposed to doxorubicin but were treated with daunorubicin or chest radiotherapy. HS3ST4 was significantly upregulated (P=4.7x10-6) in response to doxorubicin treatment in human induced pluripotent stem-cell-derived cardiomyocytes from patients with cardiomyopathy.

Conclusions: We identified and replicated a novel locus for doxorubicin-induced cardiomyopathy which was associated with increased risk in survivors of European ancestry but decreased in their Afr can counterpart.