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Title: 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.

Background: Treatment of childhood cancer using doxorubicin is associated with a well-established dose-related risk of cardiomyopathy, which can lead to heart failure and affects ~7-10% of exposed children and adolescents. Here, we identified a genetic variant associated with risk of doxorubicin-induced cardiomyopathy (diCM) in survivors of childhood cancer.

Methods: A genome-wide association study using common variants (MAF≥5%; whole-genome sequencing data) was performed among 993 SJLIFE survivors of European ancestry (median age, 36.6 years; range, 8.7-62.2 years) treated with doxorubicin only (210 with diCM; defined as CTCAE grade ≥2 clinically assessed cardiomyopathy). Replication analyses were performed separately among 1,430 CCSS survivors of European ancestry (median age, 35.4 years; range, 15.8-60.7 years) and 159 SJLIFE survivors of African ancestry (median age, 32.6 years; range, 8.9- 61.1 years) exposed to doxorubicin only. Analyses were adjusted for age at primary cancer diagnosis, sex, doxorubicin dose, age at last contact and top five principal components.

Results: We identified a genome-wide significant association between a novel locus near *HS3ST4* and diCM risk in SJLIFE survivors of European ancestry (rs112474856; OR=2.78; $P=3.3\times10^{-8}$). This association replicated in CCSS survivors of European ancestry (OR=1.74, $P=0.036$) 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 diCM risk in two independent datasets including survivors of European ancestry in SJLIFE (OR=1.20; $P=0.71$) and CCSS (OR=1.02; $P=0.98$) who were not exposed to doxorubicin but were treated with daunorubicin or chest radiotherapy, suggesting doxorubicin specificity. No association was observed between rs112474856 and risks of cardiomyopathy (OR=1.00; $P=0.88$) or heart failure (OR=1.00; $P=0.59$) in 361,194 UK Biobank participants from the general population. *HS3ST4* was significantly upregulated ($P=4.7\times10^{-6}$) in response to doxorubicin

treatment in human induced pluripotent stem-cell-derived cardiomyocytes from patients with diCM. *HS3ST4* encodes heparan sulfate, the latter was recently linked to immune activation, cardiac fibrosis, and heart failure.

Conclusions: Leveraging the two largest cohorts of childhood cancer survivors in North America, we identified and replicated a novel locus for diCM which was associated with increased risk in survivors of European ancestry but decreased in their African counterpart.