GENOME-WIDE ASSOCIATION STUDY TO IDENTIFY OBESITY SUSCEPTIBILITY LOCI IN SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): A REPORT FROM THE CHILDHOOD CANCER SURVIVOR STUDY (CCSS)

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Background/Objectives: Obesity is an important late effect among survivors of childhood ALL. Although numerous body mass index (BMI) susceptibility variants have been identified in the general population, genetic predisposition for obesity in ALL survivors remains poorly understood. We conducted a GWAS of BMI among ≥5-year survivors of ALL from the CCSS and Texas Children's Cancer Center (TCCC).

Design/Methods: The discovery GWAS included 1,114 adult survivors of ALL participating in the CCSS, genotyped on the HumanOmni5Exome array and imputed using the 1000 Genomes Project. Independent replication sets from TCCC, genotyped on the Illumina OmniExpress array, included: 1) 148 adult survivors and 2) 312 survivors <20 years of age with BMI z-scores calculated from age- and sex-specific growth charts. In separate models for each population, BMI or BMI z-score was regressed on age at diagnosis, age at follow-up, cranial radiotherapy (CRT), sex, and age at diagnosis-CRT interaction. Resulting residuals were included as the dependent variable in linear regression models to estimate the beta and *P*-value for each SNP, adjusting for genotype-derived principal components. For SNPs associated with BMI ($P<10^{-6}$) in the discovery set, meta-analyses were conducted across the three populations using an inverse-variance-based approach.

Results: We first evaluated ~100 BMI-associated SNPs identified from GWAS in the general population. None were associated with BMI among ALL survivors after correcting for multiple comparisons. In the meta-analysis, we identified a putative locus on 16p13.3 that reached genome-wide significance ($P=8.5\times10^{-9}$) with consistent beta estimates across the three populations: 0.20 (CCSS); 0.16 (TCCC 1); and 0.27 (TCCC 2). In GTEx, SNPs in this locus are associated with *DECR2* expression across multiple tissues, which has been implicated in lipoprotein metabolism.

Conclusion: We identified a potentially novel BMI-associated locus on chromosome 16 in ALL survivors. Additional analyses are underway, including further replication, estimation of polygenic risk scores, and investigation in high-risk treatment groups.