

A genome-wide association study (GWAS) of body mass index (BMI) in adult survivors of childhood acute lymphoblastic leukemia (ALL): A report from the Childhood Cancer Survivor Study (CCSS) and St. Jude Lifetime Cohort (SJLIFE)

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**Background:** Obesity is an important late effect in survivors of childhood ALL. Many genetic variants are associated with BMI in the general population, yet genetic predisposition for obesity in ALL survivors is poorly understood. We conducted a GWAS of BMI among ALL survivors from the CCSS and SJLIFE.

**Methods:** The GWAS discovery analysis included 1,458 ALL survivors in the CCSS. Replication included 398 independent subjects from SJLIFE. BMI ( $\text{kg}/\text{m}^2$ ) was regressed on additive variants adjusted for age at diagnosis, age at follow-up, treatment (yes/no) with cranial radiotherapy (CRT), sex, and genotype-derived principal components. Additional analyses were conducted stratifying on CRT, a risk factor for obesity among survivors. In addition, we used inverse-variance weighted meta-analyses to combine the CCSS and SJLIFE effect estimates for SNPs potentially associated with BMI ( $P < 10^{-7}$ ) in the CCSS.

**Results:** We identified 23 SNPs in 17 loci associated with BMI at  $P < 10^{-7}$  in CCSS. However, only one SNP replicated ( $P = 0.01$ ) in SJLIFE (**Table**). This variant, rs113934659, was strongly associated with BMI among subjects not treated with CRT ( $6.1 \text{ kg}/\text{m}^2$  per T allele,  $P_{\text{Meta}} = 2.4 \times 10^{-9}$ ) and mapped to an intron in *LEFTY1*, which encodes a TGF-beta ligand and is primarily expressed in the colon and pancreas. Based on bioinformatics data from ENCODE, rs113934659 is located in an enhancer chromatin state in gastric tissue and the endoderm.

**Conclusions:** We identified a potentially novel genetic locus of low frequency with large effect sizes for BMI in survivors of childhood ALL. Notably, *LEFTY1* rs113934659 may regulate gene transcription in the gastrointestinal tract.

SNP	Locus	Risk Allele	CCSS AF	CCSS beta	CCSS P	SJLIFE beta	SJLIFE P	Meta beta	Meta P
<b>Overall GWAS</b>									
rs189224538	<i>CYP7B1-LINC00251</i>	G	0.007	7.3	6.0E-9	1.0	0.72	6.3	3.9E-8
<b>CRT-yes</b>									
rs149426421	<i>U6-KCNMB2</i>	T	0.011	6.7	9.4E-8	12.4	0.07	6.9	1.9E-8
rs575792008	<i>LINC00856</i>	A	0.006	7.5	9.4E-8	10.8	0.12	7.7	2.3E-8
<b>CRT-no</b>									
rs113934659	<i>LEFTY1</i>	T	0.024	6.7	9.1E-8	4.8	0.01	6.1	2.4E-9