Population-based Genetic Risk Loci and the Risk for Diabetes Mellitus in the Childhood Cancer Survivor Study (CCSS)

Rathore N[1], Richard M[1], Armstrong G[2], Brown A[1], Friedman D[3], Hanis C[4], Kamdar K[1], Leisenring W[5], Machiela M[6], Meacham L[7], Morton L[6], Mostoufi-Moab S[8], Chanock S[6], Oeffinger K[9], Robison L[2], Scheet P[10], Sklar C[3], Yasui Y[2], Bhatia S[11], Lupo P[1]

[1]Baylor College of Medicine, [2]St. Jude Children's Research Hospital, [3]Memorial Sloan Kettering Cancer Center, [4]University of Texas Health Science Center at Houston, [5]Fred Hutchinson Cancer Research Center, [6]National Cancer Institute, [7]Emory University School of Medicine, [8]Children's Hospital of Philadelphia, [9]Duke University, [10]MD Anderson Cancer Center, [11]University of Alabama at Birmingham

Background: Genome-wide association studies (GWAS) have identified over 60 germline susceptibility loci for diabetes mellitus (DM) in the general population. However, these variants have not been systematically evaluated among childhood cancer survivors. Therefore, we assessed the role of known DM-associated genetic variants, individually and as a genetic risk score (GRS), on DM risk in childhood cancer survivors.

Methods: The study population consisted of 4,804 childhood cancer survivors of European ancestry enrolled in the CCSS, 360 of whom self-reported incident DM and consistent medication use. We identified 62 variants associated with DM ($P<5.0x10^{-8}$) in two population-based GWAS: DIAGRAM and the UK Biobank (UKBB). We used multivariable logistic regression to evaluate for the association between each individual DM variant and DM risk in the CCSS. We further estimated the OR for DM using a GRS, calculated from the unweighted sum of risk alleles across the 62 variants. All models were adjusted for relevant DM demographic and treatment characteristics previously identified in the CCSS (see Table footnote).

Results: Among the 62 population-based DM-associated variants, 45 had the same direction of effect in the CCSS, of which six also achieved $P<0.05$ (**Table**). We identified a significant association of the GRS, derived from 62 population-based GWAS variants, with incidence of DM among childhood cancer survivors (OR=1.06, 95% CI=1.03-1.08, $P=1.2x10^{-5}$). Furthermore, survivors with a GRS in the highest quartile were 1.89 times (95% CI=1.34-2.66, P=0.0003) more likely to develop DM compared to survivors in the lowest quartile of the GRS.

Conclusion: We found that a GRS calculated from population-based DM susceptibility loci was associated with increased DM risk in survivors of childhood cancer. This information could be leveraged to identify childhood cancer survivors at highest risk for DM who could benefit from early interventions after therapy.

Table. Significant population-based DM-associated variants and DM risk in the CCSS

		Population-based GWAS					CCSS		
Variant	**Locus**	**Study**	**Risk Allele**	**OR**	**95% CI**	**P-value**	**OR***	**95% CI**	**P-value**
rs6757251	*THADA* intron	DIAGRAM	C	1.139	1.093-1.187	1.9E-10	1.51	1.38-1.64	0.007
rs2972145	*MIR5702*	UKBB	C	1.003	1.002-1.004	6.3E-11	1.24	1.17-1.31	0.014
rs116647495	*ITPR3* intron	UKBB	C	1.009	1.006-1.012	1.2E-08	1.61	1.43-1.79	0.022
rs2258238	*HMGA2* intron	UKBB	T	1.005	1.003-1.006	1.9E-09	1.28	1.18-1.38	0.039
rs4239217	*HNF1B* intron	UKBB	G	1.003	1.002-1.004	1.5E-12	1.20	1.13-1.27	0.028
rs2023681	*HORMAD2-LIF*	DIAGRAM	G	1.127	1.082-1.175	3.9E-09	1.44	1.29-1.58	0.032
GRS** with 62 variants							1.06	1.03-1.08	1.2E-05
Quartile 1							Ref		
Quartile 2							1.22	0.88-1.71	0.2378
Quartile 3							1.60	1.13-2.26	0.0083
Quartile 4							1.89	1.34-2.66	0.0003

*Adjusted for body mass index, age at follow-up, sex, genotype-derived principal components of ancestry, cancer diagnosis, decade of diagnosis, alkylating chemotherapy (yes vs. no), and abdominal radiation (yes vs. no)
**Continuous GRS