Title: Genetic Architecture of Diabetes Mellitus in Long-term Survivors of Childhood Cancer

Working Group: Genetics
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Background & Rationale:
Diabetes mellitus (DM) is a complex heritable metabolic disorder characterized by insulin resistance (type 2) or insulin deficiency (type 1). In the general population, DM is associated with significant morbidity including retinal disease, chronic renal insufficiency, neuropathy, cardiovascular disease, and premature death.[1] Confirmed by several recent studies, survivors of childhood cancer demonstrate an elevated risk of DM.[2-10] Despite being a serious late effect of cancer therapy, the mechanisms underlying individual susceptibility to DM remain incompletely understood, thereby, limiting prevention efforts. Therefore, the objective of this study is to identify inherited genetic variation associated with the incidence of DM among childhood cancer survivors enrolled in the Childhood Cancer Survivor Study (CCSS).

Diabetes Mellitus in Childhood Cancer Survivors: A recent report by Mostoufi-Moab et al. using data from the CCSS indicated that the risk of DM was nearly two times higher in survivors compared with siblings (relative risk=1.9, 95% confidence interval [CI]: 1.6-2.4).[11] Notably, the risk of DM in survivors of childhood cancer appears to be greatest among those treated with abdominal irradiation and/or total body irradiation (TBI). Two studies reported an increased risk of DM in children with Wilms tumor treated with abdominal irradiation,[3,10] and several studies identified an increased prevalence of DM among survivors exposed to TBI as part of preconditioning regimen for allogeneic bone marrow transplantation (BMT).[2,4,5,7-9] Data from the CCSS provide additional evidence that childhood cancer survivors exposed to abdominal irradiation have an increased risk of DM.[6] Compared to unaffected sibling controls, survivors of high-risk neuroblastoma were 7-times more likely to report DM (odds ratio [OR]=6.9, 95% CI: 3.5-13.9), whereas survivors of Wilms tumor and Hodgkin lymphoma (HL) were twice as likely to report DM (OR=2.1, 95% CI: 1.1-4.0 and OR=2.1, 95% CI: 1.2-3.5, respectively). Furthermore, among these same cancer diagnoses, there was no increased risk of DM in survivors who were spared abdominal irradiation. Among those who received TBI, there was also a strong and increased risk of DM compared to siblings (OR=12.6, 95% CI: 6.2-25.3), particularly among survivors of acute myeloid leukemia (AML) exposed to TBI (OR=17.7, 95% CI: 6.4-49.4).[6] Among those with DM, it was estimated that at least 80% of survivors had type 2 DM based on glycemic agents used for treatment.

As the risk of type 2 DM is potentially modifiable, it is critical to better characterize mechanisms of susceptibility among childhood cancer survivors and identify high-risk individuals who may benefit from targeted intervention. However, in spite of the clinical significance of DM and the strong risk among certain groups, it remains largely unknown why some survivors exposed to abdominal irradiation or TBI develop DM while others do not.

Genetic Architecture of DM: The genes most strongly associated with type 1 DM are in the human leukocyte antigen (HLA) family. Specifically, the risk of developing type 1 DM is increased by certain variants of the *HLA-DQA1*, *HLA-DQB1*, and *HLA-DRB1* genes. In fact, the HLA region explains a substantial portion of heritability and has proven to be clinically useful in distinguishing type 1 DM in specific clinical scenarios. By comparison, the genetic architecture of type 2 DM is best characterized as polygenic. Specifically, type 2 DM is a multifactorial disease with a sibling relative risk of 2 and an estimated heritability of 30-70%.[1] A great deal of progress has been made in identifying the genetic factors underlying type 2 DM through genome-wide association studies (GWAS).[1,12] Most of the known genetic association signals have been discovered in the past decade from successive GWAS of type 2 DM, which have included larger samples, denser genotyping arrays, and richer ethnic diversity (**Figure 1 and Supplemental Table 1**).[1] Few, if any, of these signals have been evaluated in relation to DM risk in childhood cancer survivors.

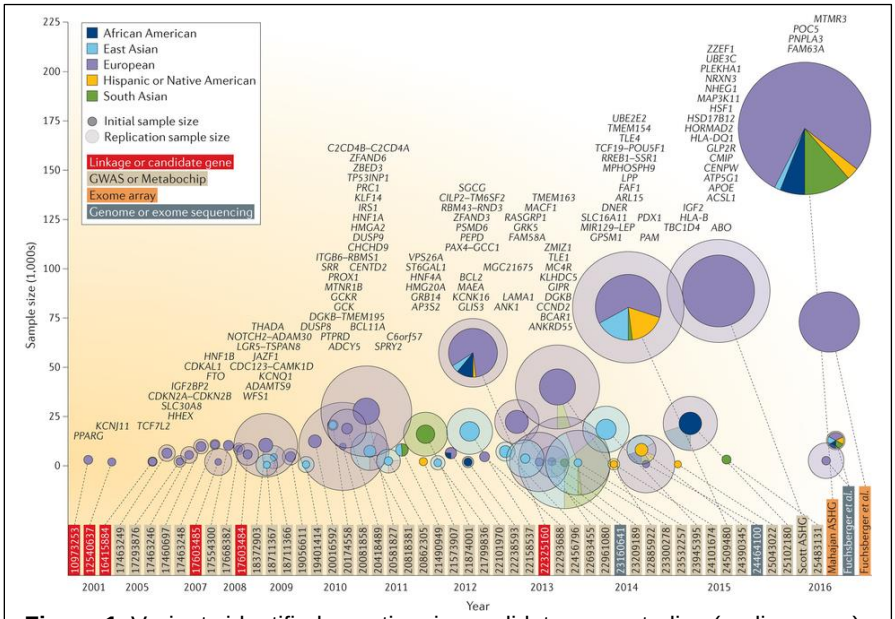

Figure 1. Variants identified over time in candidate gene studies (earlier years) and GWAS of type 2 DM (from *Nature Reviews Genetics*)

Clonal Mosaicism and Type 2 DM: Clonal mosaic events (CMEs) are defined by the presence of different karyotypes in two or more cell lineages within an individual. CMEs arise due to errors during mitosis and can lead to point mutations, aneuploidy, gain or loss of chromosomal segments, or copy-neutral loss of heterozygosity (LOH) in a subset of cells.[14] Recent studies indicate that the frequency of CMEs in DNA obtained from blood or buccal samples significantly increases with age.[13-15] Methods have been developed to detect CMEs using GWAS data. These studies suggest that the frequency of detectable CMEs in older individuals is 2-3% and sometimes higher (e.g., tenfold) based on certain aging-related phenotypes.[15] For example, one recent report indicated an association between detectable CMEs and type 2 DM (OR=5.3, $p=5.1\times10^{-5}$).[16] However, little has been done to explore the role of CMEs on aging-related phenotypes (e.g., DM) among childhood cancer survivors. Given that this population suffers from numerous treatment-related comorbidities, CMEs may provide information regarding the degree of disease burden in these individuals. Additionally, characterizing CMEs may elucidate the mechanisms of diseases, such as DM, among childhood cancer survivors who demonstrate evidence of premature aging.

We hypothesize that inherited genetic variation influences the risk of DM in childhood cancer survivors. The following specific aims provide a detailed approach to assessing the genetic basis of DM in this population. To evaluate our hypothesis, we propose the following multi-prong approach for this study: (1) replication of candidate genetic variants previously published in GWAS with *de novo* type 2 DM (see Supplemental Table 1); (2) an agnostic (GWAS) approach to examine associations between novel genetic variants and DM in childhood cancer survivors; and, as an exploratory aim, (3) use the GWAS data to determine the association between detectable clonal mosaicism and DM in childhood cancer survivors.

Primary Aims:

1. **Evaluate the role of previously published *de novo* type 2 DM genetic variants in the risk of DM in childhood cancer survivors.**
   1.a. Determine the association between previously identified type 2 DM variants and reported DM in CCSS survivors of European ancestry.

   1.b. Determine the role of type 2 DM gene-treatment (abdominal irradiation and/or TBI) interactions on subsequent diagnosis of DM in CCSS survivors of European ancestry.

1.c. Evaluate the utility of a polygenic risk score using previously published *de novo* type 2 DM genetic variants for identifying childhood cancer survivors at the greatest risk of developing DM.

2. **Identify novel genetic variants associated with DM in childhood cancer survivors.**
   2.a. Identify genetic variants associated with reported DM among CCSS survivors of European ancestry (Discovery Population) using a genome-wide approach and independently replicate novel associations (see Replication).

   2.b. Determine the role of novel gene-treatment interactions (abdominal irradiation and/or TBI) on DM in CCSS survivors of European ancestry.

Exploratory Aim(s):

1. **Compare the presence of clonal mosaic events among childhood cancer survivors with and without DM.**
   1.a. Evaluate the presence of detectable clonal mosaic events using data from the Illumina HumanOmni5Exome array on CCSS survivors with and without DM.

   1.b. Evaluate the association between clonal mosaicism and DM in childhood cancer survivors.

Analysis Framework:
This analysis will utilize existing data within the CCSS to address each specific aim. The proposed study population, variables of interest, and analytic plan for each aim are outlined below. Final decisions on the methods will be reached with input from CCSS statisticians and collaborators:

Outcomes of Interest: The primary outcomes of interest will be based on (1) self-report of being told by a physician that they had diabetes and (2) self-reported use of medication for diabetes obtained from CCSS Original Cohort questionnaires (Baseline or Follow-up 1 – Follow-up 5). Related to DM medication use, participants were asked if they had taken insulin or an oral medication for DM for more than 1 month in the preceding 2 years. For this analysis, DM will be dichotomized (yes/no). Ultimately, the same definitions of DM used in previous assessments will be used in this study.

Study Population: The study population will consist of the 5,324 childhood cancer survivors of European ancestry enrolled in the Original CCSS Cohort (diagnosed 1970-1986) with available genotype data. In this eligible population, there are 189 survivors with self-reported DM as of the June 1, 2017 data release. We will conduct secondary analyses restricted to high-risk sub-population survivors: (1) abdominal irradiation (not including TBI) and (2) TBI.

Exploratory Variables: As outlined in the analytic approach for each specific aim, the primary exploratory variables are genotypes obtained from Illumina HumanOmni5Exome array. As genotype data available on those who received TBI and allogenic BMT may represent donor DNA, we will only use genetic data from those subjects if genotypes were estimated using buccal DNA from mouthwash kits, which should represent the survivors inherited DNA.

Additional Covariates considered in the analysis will include:

- Cancer diagnosis
- Year of cancer diagnosis
- Age at cancer diagnosis
- Age at Baseline and Follow-up 1 – Follow-up 5
- Gender
- Genetically determined ancestry (calculated ancestry–specific principal components)
- Height at Baseline and Follow-up 1 – Follow-up 5
- Weight at Baseline and Follow-up 1 – Follow-up 5
- Education at Baseline and Follow-up 1 – Follow-up 5
- Household income at Baseline and Follow-up 1 – Follow-up 5

- Behavioral risk factors (i.e. physical activity measures [to be more fully explored with help of CCSS biostatisticians] and smoking status) Baseline and Follow-up 1 – Follow-up 5
- Radiation therapy field (any, brain, abdominal, and total body) and dose
- Chemotherapy (any, alkylating agents, anthracyclines, corticosteroids) and dose (for alkylating agents and anthracyclines)

Analytic Approach: Descriptive statistics will be generated and compared between survivors of childhood cancer with and without the outcome of interest (DM). For each aim, we will conduct regression diagnostics to evaluate the assumptions and overall goodness of fit for the most significant findings. Appropriate steps will be taken to address multiple comparisons (i.e. Bonferroni-corrected p-values), influential observations, and violations of the regression model assumptions. Study characteristics will be displayed in tables such as example Table 1 at the end of the proposal.

The primary focus of Aim 1 is to test the association of genetic variants previously identified in GWAS of DM (see Supplemental Table 1). We will explore two approaches for evaluating this association in Aim 1a. First, for variants with a minor allele frequency (MAF) ≥1%, we will calculate an odds ratio (OR), 95% confidence interval (CI), and p-value for the association between each SNP and DM using multivariable logistic regression. A log-additive model of inheritance will be used unless otherwise indicated in the study question. For this analysis, statistical significance will be defined as $p<0.05$, as these variants have all been previously linked to DM in the general population. Additionally, the direction of effect and effect size will be compared with previous assessments. Second, for less common variants (MAF <1%), we will conduct exploratory analyses using the Mantel-Haenszel (MH) test statistic. We will use the MH test statistic as it is based on the exact conditional distribution, which is more appropriate when evaluating associations with less frequent genetic variants in smaller sample sizes. Results will be displayed in tables such as Supplemental Table 1. When investigating whether gene-treatment interactions underlie DM risk (Aim 1b), we will calculate a p-value for the likelihood ratio test comparing a full regression model (main effects plus interaction term) with a reduced model (main effects only). We will use a p value cut point of <0.05 to determine if significant gene-treatment interactions are present. For the polygenic risk score (Aim 1c), we will explore developing methodologies. One standard approach is to use a log-additive model of inheritance for coding all genotypes. Principal components analysis will be used to adjust for population stratification. Significant variants ($p<0.05$) will be included in the genetic risk score (GRS). The GRS will be coded 1 for the risk homozygote, 0 for the heterozygote, and -1 for the non-risk homozygote. The GRS for each individual will be created by summing values.

For Aim 2, the analytic approach will be similar to Aim 1, but the number of variants will differ. Specifically, we will calculate an OR, 95% CI, and p-value for the association between each imputed genetic variant and DM using SNPTEST v2.5.4, assuming a log-additive model of inheritance. Quality control of the imputed data set will remove data with a MAF <1% or imputation quality score (R2) <0.30. In secondary analyses (as in Aim 1), we will utilize the MH test statistic for less frequent variants (MAF <1%). In each analysis, we will evaluate potential confounding due to primary cancer diagnosis, age at cancer diagnosis, gender, age at last follow-up or time of event, and radiation site and dose. Therapeutic subgroup analyses will be restricted to the high-risk survivor populations previously identified (see Study Population). Statistical significance will be defined as a genome wide $p <5x10^{-8}$. Results will be displayed in tables (see example Table 2). When investigating novel gene-treatment interactions, we will use GxEScan, which implements an efficient 2-step method for modeling gene-environment interactions (http://biostats.usc.edu/software).

Table 2. Results from common variant analyses

Chr.	BP	SNP ID	Gene	Functional annotation	A1	A2	N	OR	95% CI	p-value
1	2345	rs6789	*ABC*	Exonic	A	C	5324	2.5	1.6-3.4	$1x10^{-4}$

Chr.=chromosome; BP=base pair; SNP ID=single nucleotide polymorphism identifier; A1=allele 1; A2=allele 2

For the Exploratory Aim, we will work closely with collaborators at the National Cancer Institute. We first propose assessing the presence of CMEs (of ≥2 Mb in length) using Illumina HumanOmni5Exome arrays in DNA obtained from all participants. We will explore multiple methods to detect CMEs. For example, in one approach, to detect CMEs with these specific arrays and classify them (as copy-gain, copy-loss, or copy-neutral CMEs) with an estimated percentage of abnormal cells, we will use the algorithm proposed by Jacobs et al.,[14] which was based on the B-allele frequency measurement and the log relative probe intensity ratio. We will also use haplotype-based profiling to detect allelic imbalance, which has been demonstrated to detect smaller CMEs and the presence of aberrant cells in proportions <0.25% of sample (and was developed by Dr. Scheet, Co-I).[18] Logistic regression will then be used to detect the association between CMEs and type 2 DM, adjusting for the covariates identified in Aims 1 and 2. As part of this assessment, we will evaluate the associations between key treatment exposures on CMEs in this population.

Power: Power to detect associations between common SNPs (MAF range 10% to 40%) and DM in the discovery population (i.e., CCSS Original Cohort) assuming a log-additive model of inheritance for Aims 1 and 2 were calculated using Quanto Version 1.2.4. Other inputs included 189 cases; 5,135 controls; alpha=6×10^{-4} (assuming ~80 variants from previous GWAS) for Aim 1; alpha=5×10^{-8} (genome-wide level significance) for Aim 2; and beta=0.80. Specifically, minimum detectable ORs are presented in Table 3. While these effect sizes are larger than seen in GWAS of *de novo* type 2 DM, we anticipate relatively strong effects based on GWAS of other late effects (e.g., hazard ratio=4.5 for GWAS of hearing loss).[17] Therefore, we should have sufficient power (>0.80) to evaluate the proposed SNP-DM associations. For the Exploratory Aim, assuming the following inputs: 2% prevalence of CMEs in a general aging population; 189 cases; 5,135 controls; alpha=0.05; and beta=0.80, we will have sufficient power to detect an OR >3.0, which is in keeping with the OR reported for CMEs on type 2 DM in the assessment by Bonnefond et al. (OR=5.3).[16]

Special Considerations:

Replication: We have identified four populations for replicating the top candidate loci identified in the discovery GWAS (Aim 2). To ensure extensive interactions, key investigators from each study (as noted below) have been included as collaborators on this proposal. Our replication populations include: *(1) Bone Marrow Transplant Survivor Study (BMTSS)* – a retrospective cohort study of patients who received blood or marrow transplantation at City of Hope, Duarte, California; or University of Minnesota, Minneapolis; or University of Alabama at Birmingham (UAB) between 1974 and 2014. There are currently 150 patients who developed DM after autologous BMT. We will select 300 survivors without DM based on the same variables identified for the CCSS analysis. This will serve as the primary replication population. Dr. Bhatia (co-principal investigator [PI] on this application) is the PI of the BMTSS and will facilitate replication activities. *(2) Texas Children's Cancer Center Long-Term Survivor (LTS) Study* – an ongoing cohort study of long-term survivors followed at Texas Children's Cancer Center. Enrollment on the protocol began in 2005, and there are currently samples available on >1,500 survivors. With an overall 2% prevalence of DM in a childhood cancer survivor population, we currently have 30 cases. Dr. Lupo (co-PI on this application) is the co-PI of the LTS Study. *(3) St. Jude LIFE Study* – an ongoing cohort of 3,006 long-term survivors being following at St. Jude Children's Research Hospital. There are currently 760 participants in the St. Jude LIFE Study who have an abnormal glucose metabolism based on clinical assessment. Dr. Robison (co-investigator on this application) will facilitate the incorporation of data from this assessment. *(4) CCSS Expansion Cohort* – a total of 10,002 childhood cancer survivors diagnosed between 1987 and 1999 are included in the CCSS Expansion Cohort. While these data will not be available immediately (anticipated completion date of sequencing for Expansion Cohort is Fall 2018), they will serve as an alternative replication population. Assuming an overall 2% prevalence of DM in a childhood cancer survivor population, we anticipate 146 (39 treated with abdominal irradiation; 107 not treated with abdominal irradiation). Dr. Armstrong (co-investigator) will facilitate the incorporation of data from this assessment. For the replication analysis, we plan to genotype samples collected on survivors in the replication populations on an Illumina Infinium iSelect HD Custom BeadChip to replicate the top variants identified in the discovery population. Depending on the results of the discovery analysis, we anticipate replicating <100 variants. This panel will include the top genetic variants from the discovery analysis as well as genetic content to identify potential duplicate samples and determine genetic ancestry

Table 3. Power to detect SNP-DM associations in Aim 1 (candidate SNP) and Aim 2 (GWAS) analysis. Minimum detectable ORs are presented for a range of MAFs.

MAF	Aim 1	Aim 2
0.10	1.90	2.50
0.20	1.70	2.15
0.30	1.62	2.00
0.40	1.60	1.98

of the survivors. For cohorts where genotype data are or will be available (St. Jude LIFE and the CCSS Expansion), we will evaluate our top variants with those existing data.

Functional Validation: We will pursue a three-tiered approach after the completion of this study. *First*, we will attempt to validate any genetic variants through the use of existing data sources. For example, if the variants associated with DM in survivors of childhood cancer have been previously identified for *de novo* DM, we will evaluate any functional evidence available for those variants, especially considering the treatment exposures. For novel variants, we will determine if there are associations with whole blood and tissue-specific gene expression (i.e., expression quantitative trait loci or eQTLs) using data available from The International HapMap Project, the Gene Expression Omnibus (GEO), Genotype-Tissue Expression (GTEx), and other resources. *Second*, we will identify appropriate preclinical models for functional validation. *Third*, we will begin characterizing intermediate phenotypes (e.g., impaired glucose tolerance) in high-risk populations currently being followed at Texas Children's Cancer Center (those treated with abdominal irradiation and/or TBI) to evaluate the impact of SNPs identified on these intermediate phenotypes.

Table 1. Characteristics of childhood cancer survivors who were exposed to TBI and/or abdominal irradiation who did and did not develop DM		
Characteristic	**DM (n = ____)**	**No DM (n = ____)**
Median age at diagnosis of primary cancer, years (range)		
Age at original diagnosis, years, *n (%)*		
< 5		
5 – 10		
11 – 15		
>15		
Median age at last follow-up, years (range)		
Current age, years, *n (%)*		
< 20		
20 – 29		
30 – 39		
> 40		
Median duration of follow-up, years (range)		
Sex, *n (%)*		
Males		
Females		
Race/ethnicity, *n (%)*		
White, non-Hispanic		
Black, non-Hispanic		
Hispanic, non-Hispanic		
Other		
Primary cancer diagnosis, *n (%)*		
Leukemia		
Lymphoma		
Solid Tumor (i.e. Wilms, neuroblastoma)		
Type of radiation, *n (%)*		
TBI		
Abdomen only		
Dose of radiation, *n (%)*		
0.1 – 19 Gy		
20 – 39 Gy		
> 40 Gy		
Behavioral Risk Factors, *n (%)*		
Smoking status		
Physically active		
Weight at Baseline, kilograms, *n (%)*		
<50		
50-100		
>100		
Median weight at last follow-up, kilograms (range)		
Vital status, number alive, *(%)*		

Supplemental Table 1. Top 15 known genetic loci associated with type 2 DM

Reported Gene	SNP ID	p-value	Region	Location	PMID
TCF7L2	rs7903146	4×10^{-94}	10q25.2	10:112998590	25102180
KCNQ1	rs2237892	2×10^{-42}	11p15.4	11:2818521	18711367
CDKN2A, CDKN2B	rs2383208	2×10^{-29}	9p21.3	9:22132077	19401414
CDKAL1	rs7756992	2×10^{-26}	6p22.3	6:20679478	24509480
CENTD2	rs1552224	1×10^{-22}	11q13.4	11:72722053	20581827
FTO	rs9939609	1×10^{-20}	16q12.2	16:53786615	22693455
MAEA	rs6815464	2×10^{-20}	4p16.3	4:1316113	22158537
IRS1	rs7578326	5×10^{-20}	2q36.3	2:226155937	20581827
HHEX, IDE	rs1111875	3×10^{-19}	10q23.33	10:92703125	24509480
SLC30A8	rs3802177	2×10^{-18}	8q24.11	8:117172786	24509480
IGF2BP2	rs4402960	1×10^{-17}	3q27.2	3:185793899	24509480
DUSP9	rs5945326	7×10^{-16}	Xq28	X:153634467	22961080
BCL11A	rs243021	3×10^{-15}	2p16.1	2:60357684	20581827
SLC16A13, SLC16A11	rs75493593	5×10^{-15}	17p13.1	17:7041768	24390345
MTNR1B	rs1387153	8×10^{-15}	11q14.3	11:92940662	20581827

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