Germline Pathogenic Structural Variants in 8,400 Whole Genomes of Pediatric Cancer Patients and Survivors

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Here we examined whole genome sequences (WGS) of >1,000 pediatric cancer patients enrolled in the Pediatric Cancer Genome Project and Genome for Kids research studies, >7,000 pediatric cancer survivors enrolled in the St. Jude Lifetime Cohort and Childhood Cancer Survivor Study, and 450 community controls. We aimed to determine the prevalence and spectrum of potentially pathogenic germline structural variants (SVs) (*e.g.,* deletions, inversions, insertions and translocations) in coding and noncoding regulatory regions of the genome associated with cancer predisposition. Using a copy number variant (CNV) detection algorithm and three SV detection algorithms, we identified germline SV candidates and filtered against curated public polymorphic gnomAD-SVs, CNV datasets, and control WGS data to enable removal of 70% of identified SVs deemed polymorphic or artifacts. Evaluation of additional germline variants, patient clinical and family history data and publicly available genomics data (e.g. methylation and topologically associated domains) facilitated assignment of potential pathogenicity to identified SVs.

Preliminary analysis identified >189,000 deletion SVs, an average of 20 SVs/case. Deletion SVs overlapping coding regions of 89 previously defined cancer genes (17 SVs in patients; 116 in survivors) had a prevalence of 1.4% in patients, as well as in survivors, when examined independently. When extending to an additional 933 cancer-related genes, overlapping coding deletion SVs are prevalent in 6.2% of patients versus 7.2% of survivors. Examples of potential-regulatory deletion SVs identified upstream of genes include *BRCA2* in a Hodgkin Lymphoma (HL) survivor (previous studies show HL survivors have an increased incidence of breast cancer), *NF2* in an astrocytoma survivor (a potential disease causative event), and DNA repair gene *MSH6* in an acute lymphoblastic leukemia survivor. CRISPR deletions mimicking these events are being generated in relevant cell lines to examine if downstream gene expression is affected, supporting pathogenicity. Preliminary analysis of germline internal tandem duplications (ITDs) identified an event affecting exons 5-17 of *RB1* in a bilateral retinoblastoma patient, and tumor WGS and transcriptome data support loss of the wildtype variant and ITD expression, respectively. Our data highlights the importance of examining germline SVs, providing an extensive analysis of cancer predisposition variants and suggests germline SVs may contribute to a significant number of pediatric cancers as well as secondary neoplasm development following pediatric cancer survival.

Abstracts due: Thursday June 11, 8pm ET

2,300 characters (excluding spaces) …currently at 2,362

Topic: Molecular Effects of Genetic Variation

Effects that genetic variants have on cellular or molecular traits. Content appropriate for this section includes eQTL (and other QTL) mapping of regulatory variants, functional characterization of disease-associated variants, prediction of variant effects on molecular traits, and assays for measuring regulatory or other molecular effects of genetic variant.

Subtopics:

b. cancer

Keywords (5):

14. Bioinformatics
18. Cancer
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86. Genome editing/CRISPR
87. Genome sequencing