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"Discovery of non-coding oncogenic mutations in pediatric acute lymphoblastic leukemia using ATAC-seq and Hi-C"

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SCIENTIFIC ABSTRACT
Acute Lymphoblastic Leukemia (ALL) is the most common pediatric cancer. It affects thousands of children in the United States each year. Improvements in therapy have pushed the 5-year survival rate of childhood ALL to over 90%, however the prognosis for the 10-20% of patients who relapse following treatment remains very poor. Some protein-coding mutations are known to be associated with relapse, however, for most patients the molecular basis of relapse is unknown. We hypothesize that undiscovered genetic mutations in non- coding regions of the genome are important drivers of ALL oncogenesis and relapse. Here we propose to develop new methods that use data from genome- wide chromatin assays to identify non-coding regulatory mutations in ALL tumors. Specifically, our methods will identify structural variants by performing computational and statistical analysis of data from the Assay for Transposase- Accessible Chromatin (ATAC-seq) and Hi-C experiments. We will perform ATAC- seq and Hi-C on 20 bone marrow samples from ALL patients at Rady Children's Hospital-San Diego and use our methods to discover novel regulatory mutations in these samples. Any pathogenic non-coding regulatory mutations that we discover will help illuminate the molecular causes of ALL tumorigenesis and relapse, and could eventually lead to improvements in targeted therapy.

LAY ABSTRACT
Acute Lymphoblastic Leukemia (ALL) is the most common form of cancer in children. Studies of ALL tumors have led to improved therapies, and increased long-term survival rates in children from ~58% in the 1970s to over 90% today. Yet 10-20% of ALL patients relapse following their initial treatment, and these patients have a grim prognosis with survival rates between 21% and 53%. Therefore, there is a need for improved therapies stemming from a better understanding of the molecular events that promote ALL progression and relapse. We hypothesize that some genetic mutations that are important for ALL onset and relapse have remained undiscovered because they are located in parts of the genome that are difficult to study. Specifically, most studies have focused on mutations that directly affect protein-coding genes, rather than "non-coding regulatory" mutations that affect which genes are expressed. We propose to develop new approaches to identify non-coding mutations in ALL tumors. The basis for our approach is computational analysis of data from new methods (known as ATAC-seq and Hi-C) that provide information about the location and 3D organization of non-coding regulatory sequences in the genome. We will perform ATAC-seq and Hi-C experiments on 20 ALL tumor samples from patients at Rady Children's Hospital-San Diego and use the resulting data to identify non-coding regulatory mutations. Any non-coding regulatory mutations that we discover will help illuminate the molecular causes of ALL onset and relapse, and could eventually lead to improvements in targeted therapy.