Title: Drug-response modulating genes in ETV6::RUNX1 childhood leukemia

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Abstract

ETV6::RUNX1 leukemia is the second most common subtype of childhood B cell acute lymphoblastic leukemia. Although it generally has a low relapse risk, its relatively high incidence contributes to a significant proportion of B-ALL relapses. Minimal residual disease at the end of induction therapy is a key biomarker predicting treatment outcomes, while no genomic biomarkers have been identified.

In a prior study, we used multiomic data to identify genomic features predicting therapy response in *ETV6::RUNX1* ALL. As continuation, we leveraged multiomic data and a publicly available genome-wide CRISPR screen of chemotherapy-gene interactions in REH and Nalm-6 cells to study drug-response modulating genes. In these studies, multiple gene knockouts affecting sensitivity to chemotherapeutics were identified. Comparing these findings with patient-derived data, we found that gene-level CNVs correlated poorly with treatment response, though dexamethasone-sensitizing deletions were more frequent in fast responders ($p = 0.06$). Next, we examined SNVs and InDels using whole-genome and panel sequencing from 295 patients. Treatment response was linked to mutations in transcriptional regulator and tumor suppressor genes, including driver genes *ETV6* and *NF1* and three genes (*KANSL1*, *INTS1* and *TP53*) associated to drug resistance, all of which were more common in slow responders ($p < 0.05$). *TP53* mutations are linked to multidrug resistance, whereas *KANSL1* and *INTS1* are

known as methotrexate resistance –associated mutations. In addition, higher *PREX1* mutation frequency associated with dexamethasone sensitivity among fast responders to induction therapy ($p < 0.1$).

In conclusion, mutations in transcriptional regulator and tumor suppressor genes were associated with treatment response. However, our findings also suggest that stratification based on the CRISPR screen hits alone could not distinguish suboptimal early therapy responders in our patient cohort.