RAG-mediated recombination is the predominant driver of oncogenic rearrangement in ETV6-RUNX1 acute lymphoblastic leukemia.

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Public Summary:
The ETV6-RUNX1 fusion gene, found in 25% of childhood acute lymphoblastic leukemia (ALL) cases, is acquired in utero but requires additional somatic mutations for overt leukemia. We used exome and low-coverage whole-genome sequencing to characterize secondary events associated with leukemic transformation. RAG-mediated deletions emerge as the dominant mutational process, characterized by recombination signal sequence motifs near breakpoints, incorporation of non-templated sequence at junctions, approximately 30-fold enrichment at promoters and enhancers of genes actively transcribed in B cell development and an unexpectedly high ratio of recurrent to non-recurrent structural variants. Single-cell tracking shows that this mechanism is active throughout leukemic evolution, with evidence of localized clustering and reiterated deletions. Integration of data on point mutations and rearrangements identifies ATF7IP and MGA as two new tumor-suppressor genes in ALL. Thus, a remarkably parsimonious mutational process transforms ETV6-RUNX1-positive lymphoblasts, targeting the promoters, enhancers and first exons of genes that normally regulate B cell differentiation.

Scientific Abstract:
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