Relapse-specific mutations in NT5C2 in childhood acute lymphoblastic leukemia.

Relapsed childhood acute lymphoblastic leukemia (ALL) carries a poor prognosis, despite intensive retreatment, owing to intrinsic drug resistance. The biological pathways that mediate resistance are unknown. Here, we report the transcriptome profiles of matched diagnosis and relapse bone marrow specimens from ten individuals with pediatric B-lymphoblastic leukemia using RNA sequencing. Transcriptome sequencing identified 20 newly acquired, novel nonsynonymous mutations not present at initial diagnosis, with 2 individuals harboring relapse-specific mutations in the same gene, NT5C2, encoding a 5'-nucleotidase. Full-exon sequencing of NT5C2 was completed in 61 further relapse specimens, identifying additional mutations in 5 cases. Enzymatic analysis of mutant proteins showed that base substitutions conferred increased enzymatic activity and resistance to treatment with nucleoside analog therapies. Clinically, all individuals who harbored NT5C2 mutations relapsed early, within 36 months of initial diagnosis ($P = 0.03$). These results suggest that mutations in NT5C2 are associated with the outgrowth of drug-resistant clones in ALL.