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**Relapsed-Related Genes in Childhood Acute Myeloid Leukemia Revealed by Whole Genome Sequencing of Diagnostic, Remission and Relapsed Samples**

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**ABSTRACT**

There is still a big gap in knowledge about the genomic alterations in childhood acute myeloid leukemia (AML) as most molecular events defined in children were derived from adult cohorts. Relapsed AML remains as the leading cause of cancer deaths among children. In-depth understanding of the molecular mechanisms underlying this challenging disease is pivotal toward development of new therapeutic strategies to improve patients’ outcome. Therefore, we sought to reveal the mutational landscape of relapse in childhood AML among local patients. Whole genome sequencing was performed on matched trio samples collected upon diagnosis, remission and relapse from three patients of de novo childhood AML, with cytogenetically normal karyotype, complex karyotype and core binding factor AML, t(8;21)(q22;q22) respectively. The sequencing reads were mapped to the GRCh37 using the Burrows-Wheeler Aligner, duplicate reads removal using Picard, followed by variant calling (SNPs and Indels) using GATK HaplotypeCaller. Somatic mutations were identified using MuTect, and annotated by ANNOVAR. Those possibly deleterious mutations predicted by SIFT and PolyPhen2 were then prioritized for further analysis. We achieved an average sequencing depth of 55x (165 billion bases) and 30x (90 billion bases) for the genome analysis for each of the diagnostic, remission and relapsed samples. Overall, we identified a total of 186 somatic mutations (161 missense, 8 nonsense, 6 frameshift, 11 splice-site), with 88 variants at diagnosis (20-39 mutations per patient) and 98 variants at relapse (15-50 mutations per patient). Of the 186 non-synonymous mutations, 16 somatic variants in ETV6, EZH1, EDARADD, RYR2, PKHD1, PLXNA1, PRR13, RBM10, SH2B1, ABCG8, TAS2R7, TUBA3D, CLEC18C, RFPL4A, ADRA1A, and BAGE2, BAGE5, BAGE4, BAGE3 were present in both diagnostic and relapse samples, with recurrent mutation in 2 patients for the ETV6 gene. We have uncovered the mutational landscape of relapse in our local childhood AML patients and have identified mutations in key genes involved in the pathogenesis of myeloid leukaemia.