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GERMLINE CHEK2 P.ILE157THR VARIANT IN PEDIATRIC RELAPSED ACUTE LEUKEMIA

Background. The CHEK2 gene encodes a key kinase involved in DNA damage response, cell cycle regulation, and maintenance of genomic stability. Pathogenic variants in CHEK2 have been associated with increased susceptibility to a range of solid tumors and some hematological malignancies. However, the contribution of the CHEK2 mutations to relapse risk and disease progression in oncohematological disorders remains insufficiently characterized. **Methods.** Bone marrow specimens from 19 pediatric patients with relapsed acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) were analyzed. The cohort comprised patients with previously identified genetic relapse-risk markers as well as marker-negative cases. Ethics approval and informed consent were obtained. Germline CHEK2 variants were assessed using the AmpliSeq Hereditary Panel encompassing 59 genes. DNA libraries were sequenced on the Ion S5 Plus platform, with variant filtering and pathogenicity classification performed via Franklin by Genoox. **Results.** The pathogenic CHEK2 variants were identified in 3 of 19 samples (15.8%), comprising one AML and two ALL cases. Notably, all three harbored the identical CHEK2 p.Ile157Thr substitution, with variant allele frequencies of 0.51, 0.43, and 0.48, consistent with heterozygous germline origin. This variant co-occurred with established relapse-associated somatic markers in two cases: IKZF1 deletion in one ALL patient and monosomy 7 in one AML patient. Conversely, one relapsed ALL case carrying CHEK2 p.Ile157Thr demonstrated a cytogenetic profile associated with favorable prognosis, including moderate hyperdiploidy and the ETV6::RUNX1 fusion transcript. **Conclusions.** The recurrent germline CHEK2 p.Ile157Thr variant identified in patients with both high- and low-risk genetic backgrounds suggests a complex, context-dependent contribution of CHEK2 to leukemogenesis. Its co-occurrence with established cytogenetic and molecular abnormalities may indicate interactions between germline susceptibility and somatic events. Larger studies are needed to clarify the prognostic significance of CHEK2 variants in pediatric acute leukemias and their role in relapse.

Keywords: germline variants; relapse.

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