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Acute Leukemias

GERMLINE AND SOMATIC COHESIN GENES ALTERATIONS IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction: Leukemia is a complex disease whose molecular mechanisms of malignant transformation are not fully understood. Cohesins are essential proteins forming a complex with key roles not only in canonical DNA binding and chromosome segregation but also in non-canonical regulation of gene expression in both proliferating and post-mitotic cells. Alterations or mutations in genes encoding cohesin components may impair chromosomal stability and contribute to leukemia pathogenesis. Somatic cohesin mutations have been reported in myeloproliferative disorders, pediatric Acute Myeloblastic Leukemia (AML) and pediatric Acute Lymphoblastic Leukemia (ALL), whereas germline mutations cause Cohesinopathies such as the Cornelia de Lange Spectrum (CdLSp). Although cancer prevalence in CdLSp remains uncertain, recent studies suggest a potential predisposition to leukemia and brain tumors. Our previous report of a patient affected by both CdLSp and ALL indicated a possible involvement of germline cohesin mutations in ALL pathogenesis.

Methods: We performed Next-Generation Sequencing (NGS) RNA-Seq transcriptomic analysis of 711 consecutive diagnostic and 138 relapse samples of pediatric B/T-ALL (AIEOP-BFM protocol, Italian centers). A custom computational pipeline was developed, including DRAGENTM, fusion detection tools, B-ALL subtype classification, and Differential Expression Analysis. Additional data from both pediatric and adult ALL cohorts were integrated through an international collaboration. Fusion transcripts and germline variants were validated using real-time qPCR.

Results: Targeted NGS screening of 120 consecutive pediatric ALL cases identified 11 germline cohesin mutations: 6 missense, 4 in 3′ or 5′ UTRs, and a splice-acceptor variant. RNA sequencing of engineered LCLs revealed 619 differentially expressed genes compared to controls, many involved in key intracellular pathways, suggesting functional disruption due to mutation. Cancer prevalence was also assessed in CdLSp patients, and cohesin variants were analyzed in ALL and pediatric brain tumors. Although no significant increase in cancer incidence was confirmed, low-pathogenic germline cohesin variants might still contribute to tumorigenesis. The computational pipeline for RNA-Seq identified fusion transcripts in 6 B-ALL cases (0.7%), involving STAG1 (n=1), STAG2 (n=4), and NIPBL (n=1). Further analyses of international datasets revealed 9 additional fusions (STAG2 n=6, NIPBL n=3). Whole Genome Sequencing is in progress.

Conclusions: Our results clarify the contribution of germline and somatic cohesin alterations to pediatric ALL and highlight their non-canonical roles, supporting the identification of a novel rare molecular subgroup of leukemia within the pediatric population.