XIX CONGRESSO NAZIONALE SIES2026
Firenze | 4-6 marzo 2026
Palazzo degli Affari

XIX Congress of the Italian Society of Experimental Hematology ABSTRACT N. P047

Acute Leukemias

NGS ANALYSIS IN ACUTE MYELOID LEUKEMIA: IMPLICATIONS FOR THE IDENTIFICATION OF PREDISPOSING GERMLINE VARIANTS

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Introduction: The diagnosis of acute myeloid leukemia (AML) is currently supported by molecular investigations based on next generation sequencing (NGS) to identify somatic variants in “driver” genes, with prognostic and therapeutic implications. Some of these variants may indicate a hereditary germline predisposition, which is relevant for patient management, choice of a familial donor in case allogenic transplantation, and family surveillance strategies.
The aim of our study is the evaluation of the frequency and potential implications of germline variants in individuals with AML
Methods: Ninety-one patients with AML (80 at diagnosis, 11 at relapse) were analyzed over a 12-month timeframe using NGS with a panel of 51 genes expressed in the myeloid lineage. Based on ELN2022 recommendations, 12 of these (ANKRD26, CEBPA, CBL, DDX41, ETV6, GATA2, NRAS, KRAS, NF1, PTPN11, TP53, RUNX1) are potentially involved in the predisposition to develop hematologic diseases.
Results: We identified at least one driver mutation in 75 patients, but 32 had one or more variants with an allele frequency (VF) >45% (identified as cutoff for suspected germline variant) in one of the 12 predisposition genes. In total, we report 37 variants: 28 are classified as class I and two as class II; furthermore, seven variants of uncertain significance (class III) were reported. The most frequently implicated genes are TP53 (nine variants), RUNX1 and DDX41 (seven variants each). At the moment, only two DDX41 variants have been confirmed on DNA extracted from buccal scrubs: the presence of c.653G>A_p.(Gly218Asp) in heterozygous state was confirmed in both patients, and was subsequently detected in a family member.
Conclusions: NGS analysis in AML has the potential to identify predisposing germline variants in addition to somatic driver mutations. However, unlike solid tumors, specific recommendations for AML are not yet available. We propose a discussion on open issues including: 1) which genes to analyse for confirmatory testing, 2) which VF to use as cut-off, 3) which material is best suited for confirmatory test 4) which iter to offer to family members (both in terms of genetic counseling and monitoring for positive cases).