TAL) via Nested PCR. The products were visualized by electrophoresis, confirmed by Sanger sequencing, and the data were descriptively analyzed using R Studio 12.1 Software. **Results:** Between 2023 and 2025, a survey at HOIOL identified 220 patients diagnosed with acute lymphoblastic leukemia (ALL). Of these, 56 had a detectable molecular biomarker, although residency data were available for only 41 of these patients. These patients were distributed across 22 municipalities in Pará and the city of Macapá, in Amapá. The most prevalent fusions were *ETV6::RUNX1* (61% of cases) and *TCF3::PBX1* (23% of cases). The city of Belém had the highest concentration of cases, with varied fusions: *ETV6::RUNX1* (7), *BCR::ABL* (1), and *TCF3::PBX1* (1). The municipalities of Ananindeua, Santo Antônio do Tauá, and São Félix do Xingu each presented cases of *TCF3::PBX1* (1) and *ETV6::RUNX1* (1), while Barcarena recorded *BCR::ABL* (1) and *TCF3::PBX1* (1) fusions. Cases exclusively involving the *ETV6::RUNX1* fusion were identified in Abaetetuba (2), Afuá (1), Ajuruteua (1), Canaã dos Carajás (1), Paragominas (1), Parauapebas (1), Porto de Moz (1), Viseu (1), and Macapá (4). In turn, single occurrences of the TCF3::PBX1 fusion were observed in Cametá (2), Bragança (1), Novo Repartimento (1), and Portel (1). Additionally, Capanema and Marabá each presented one case with the *SIL::TAL* fusion, and finally, the city of Moju recorded a single case with the *KMT2A::AFF1* fusion. **Discussion and conclusion:** Notably, the southeastern region of Pará (Parauapebas, Canaã dos Carajás, Marabá, Novo Repartimento, São Félix do Xingu), an area of intense mining activity, accounted for 17% of cases with poor-prognosis fusions. The recurrence of these alterations raises the hypothesis of an association with environmental exposure to heavy metals, although a direct causal relationship cannot be established. Similarly, the northeastern region of Pará (Abaetetuba, Moju, and Cametá), characterized by intensive agricultural activity, presented 9% of cases with poor-prognosis fusions, suggesting a possible link to pesticide exposure, though a causal link has not been proven. Belém, in turn, had the highest number of cases, predominantly of good prognosis, a fact that may be attributed to its large population and proximity to reference centers, which facilitates detection. The occurrence of severe leukemia in Pará, in mining and agribusiness areas, suggests a strong link with environmental factors and demands further investigation.

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GERMLINE PREDISPOSITION TO MYELOID MALIGNANCIES: A COMPREHENSIVE ANALYSIS OF CEBPA, DDX41 AND RUNX1

D Kusma-Wosniaki [a], B Nichele-Kusma [a], H Kaur [b], E Batista-Mendes [a], M Nóbrega-Aoki [a], DL Zanette [a], JM Capo-Chichi [b]

[a] *Laboratory for Applied Science and Technology in Health, Instituto Carlos Chagas (ICC), Fundação Oswaldo Cruz (Fiocruz), Curitiba, Brazil*
[b] *Division of Clinical Laboratory Genetics, Laboratory Medicine Program, University Health Network, Toronto, Canada*

Introduction: Myeloid malignancies such as acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) are typically sporadic, but germline predisposition involving genes like CEBPA, DDX41, and RUNX1 is increasingly recognized. However, the interplay between germline and somatic events in these genes remains incompletely understood. **Objectives:** To investigate the prevalence, co-variant patterns, and clonality of pathogenic and likely pathogenic variants in CEBPA, DDX41, and RUNX1 in patients with myeloid malignancies. **Material and methods:** We analyzed 2,437 patients diagnosed with AML, MDS, MDS/AML, or myeloproliferative neoplasms (MPN). DNA from peripheral blood or bone marrow was sequenced using targeted NGS, covering 63 genes. Variants were processed using validated bioinformatic pipelines and classified per CAP/AMP/ASCO guidelines. **Results:** Among the cohort, AMP/ASCO Tier-1 and Tier-2 variants were most frequently detected in RUNX1 (9.97%, n = 243), followed by CEBPA (3.94%, n = 96) and DDX41 (2.63%, n = 64). RUNX1 mutations were commonly associated with co-occurring variants in ASXL1 and SRSF2, particularly in cases with double RUNX1 hits (37.5%). VAF distribution in double-mutated RUNX1 (RUNX1 highest hit: minimum: 10.9, maximum: 47.2, median: 38.5) with variants in ASXL1 (ASXL1 highest hit: min.: 4.3, max.: 49.5, median: 32.6 and/or SRSF2 (min.: 37.5, max.: 49.5, median: 46.1) were frequently consistent suggestive of a clonal process. CEBPA alterations with bi-allelic CEBPA variants (bZIP domain in-frame variant + an N-terminal loss-of-function variant). Co-occurring variants in GATA2 and WT1 were enriched in bi-allelic cases (60%) and were often seen at similar VAF (CEBPA bi-allelic highest hit: min.: 6, max.: 59.2, median: 41.9, GATA2 highest hit: min.: 5, max.: 50, median: 42,6; WT1 highest hit: min.: 5, max.: 94.1, median: 46.8), supporting a shared clonal origin and suggesting a distinct molecular signature potentially driving leukemogenesis. DDX41 variants showed a bimodal VAF distribution in double-mutated cases, with clusters likely suggestive of acquired (min.: 3, max.: 47, median: 6) or inherited (min.: 7, max.: 93, median: 49) variants. Unlike CEBPA and RUNX1, DDX41 variants were not associated with consistent co-variant patterns, suggestive of a different pathobiology. Of note biallelic disruptive DDX41 variants have been associated with hematologic malignancies with unique AML/MDS like features. **Discussion and conclusion:** Our findings reveal distinct mutational patterns in CEBPA, DDX41, and RUNX1, genes linked to hereditary hematologic cancers. Bi-allelic CEBPA mutations, formed a molecularly coherent subgroup frequently co-mutated with GATA2 and WT1 at similar VAFs, suggesting a shared clonal origin. Similarly, RUNX1 variants often co-occurred with ASXL1 and SRSF2 mutations, also showing consistent VAFs, though RUNX1 mutations were distributed across the gene. In contrast, DDX41 cases lacked co-variant patterns but exhibited a bimodal VAF distribution, with higher VAFs (>35%) suggestive of germline variants and lower VAFs (<20%) likely representing secondary somatic events. This study highlights the distinct biological and clinical profiles of germline and somatic variants in CEBPA, DDX41, and RUNX1, underscoring the need for further research into germline predisposition and its role in the pathogenesis of myeloid neoplasms.

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