Background

• Clonal hematopoiesis of Indeterminate Potential (CHIP) is an age-related phenomenon where somatic mutations accumulate in cells of the blood or bone marrow.1

• The presence of CHIP has been linked to an increased risk of hematologic cancers and cardiovascular disease.1

• It is a source of biological noise that causes false-positives in ctDNA analysis and is present in up to 20% of individuals over the age of 70.2

• The Signatera assay filters CHIP mutations through tumor tissue and germline sequencing thereby reducing false-positive results and focuses on tumor-specific mutations for each patient.

Methods

• Whole exome sequencing data (average depth ~250x) analyzed from buffy coat of 1104 patient.

• Variant calling was performed using Freebayes variant caller with allele frequency threshold at a frequency between1.5% and 0.5%.

• The selected variants were further screened based on the reported variants in the literature between 1% and 10%. Following which variant annotation and selection was performed based on the top 54 genes that are most implicated in myeloid disorders.

• The selected variants were further screened based on the reported variants in the literature and/or the Catalog of Somatic Mutations in Cancer (COSMIC).

• Associations with patients’ age, gender, cancer type and type of therapy were investigated, multivariate regression analysis was performed for 833 patients.

Results

• The analysis revealed an average of 0.24 (0-4) CHIP mutations per patient with an average variant allele frequency of 2.57% (1%-9.4%) (Figure 1A and 1B).

• The most common CHIP mutations were observed in DNMT3A (n=81), TET2 (n=31), and TP53 (n=31) genes (Figure 1C).

• The percentage of patients with at least 1 mutation found in DNMT3A, TET2, and TP53 were 7.34%, 2.81%, and 2.81%, respectively.

• Other genes containing CHIP mutation included NOTCH1, CDKN2A, HRAS, EZH2, ASXL1, CATA2, CKX1, CEBPA at a frequency between 0.5% and 0.5%.

• The presence of CHIP has been linked to an increased risk of hematologic cancers and the treatment. ctDNA analysis should factor these considerations in this population.

References


Conflict of Interest and Acknowledgments

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