# Characterization of Clonal Hematopoiesis of Indeterminate Potential Mutations from Germline Whole Exome Sequencing Data

Hsin-Ta Wu, Ekaterina Kalashnikova, Samay Mehta, Raheleh Salari, Himanshu Sethi, Bernhard Zimmermann, Paul R. Billings, Alexey Aleshin

Natera, Inc., San Carlos, CA, USA

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## 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 fasle-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

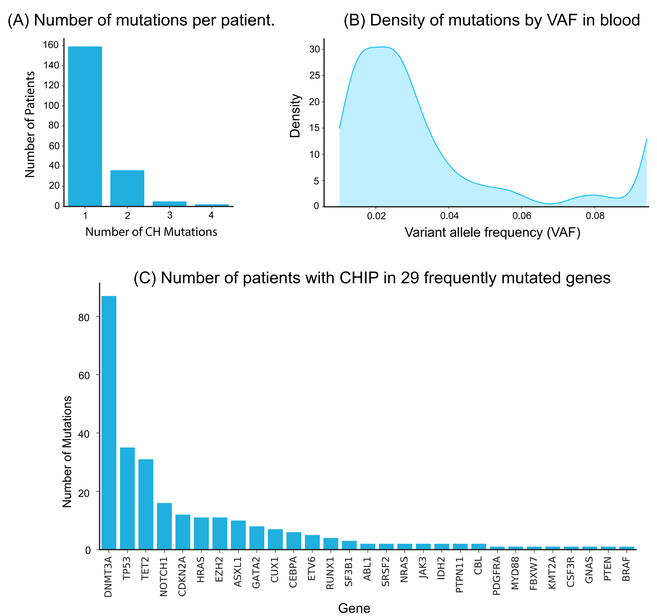
- Whole exome sequencing data (average depth ~250x) analyzed from buffy coat of 1104 patients diagnosed with various solid cancers was used to characterize CHIP mutations.
- Variant calling was performed using Freebayes variant caller with allele frequency threshold between 1% and 10%. Following which 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, GATA2, CUX1, CEBPA* at a frequency between1.5% and 0.5%.

*CHIP mutations are a common finding in the elderly population and can be influenced by the type of cancer and the treatment. ctDNA analysis should factor these considerations in this population.*

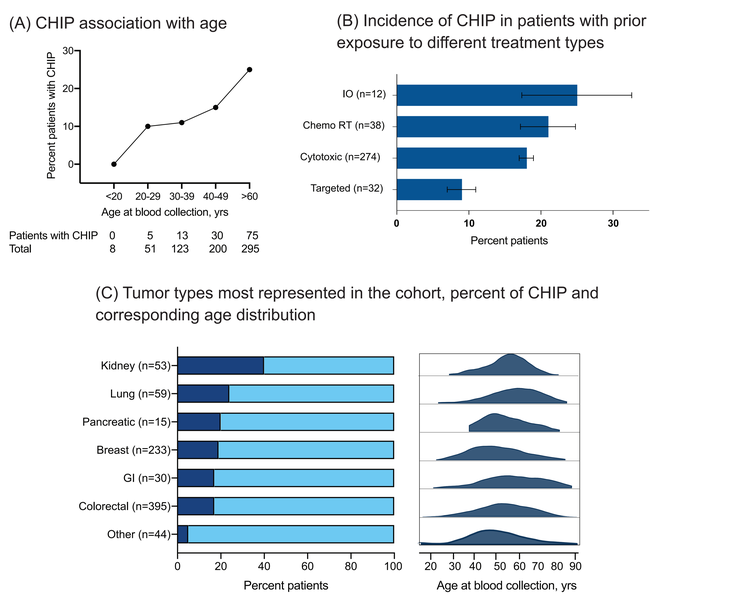
**Figure 1. Characteristics of clonal hematopoiesis mutations identified in the cohort**




## Results

- CHIP mutations were not observed in patients younger than 20 years, but they increased in frequency with every decade of life thereafter. The incidence of CHIP increased from 10% for the 20-29 years age group to 25% for age groups older than 60 years **(Figure 2A)**.
- Among patients who had undergone treatment prior to sample collection, CHIP mutation incidence was the lowest in patients treated with targeted therapy (9%), compared to those with prior exposure to to cytotoxic (18%), chemo-radiation (21%), and immunotherapy (25%) **(Figure 2B)**
- Further analysis revealed an association between incidence of CHIP and cancer type, patients diagnosed with breast (19%), pancreatic (20%), lung (24%), and kidney (40%) cancers had the highest frequency (**Figure 2C**).
- Associations between incidence of CHIP and patient's age ($p<0.0001$), kidney ($p<0.0001$), breast ($p<0.0001$) and lung ($p=0.002$) cancer type, but not gender or treatment type were significant in the multivariate regression analysis.

**Figure 2. Association of incidence of CHIP with patient age, cancer and treatment type**




### References

1. Heuser M, Thol F, Ganser A. *Deutsches Ärzteblatt International*. 2016; 113: 317–22.
2. Jaiswal S, Fontanillas P, Flannick J, et al. *N Engl J Med. 2014*; 2488-2498

### Conflict of Interest and Acknowledgments

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