Novel Associations Between Clonal Hematopoiesis and Therapeutic Exposures Revealed in Patients with Solid Tumors Using Real-World Evidence

Poster #1227

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INTRODUCTION

Clonal hematopoiesis (CH) occurs when somatic mutations confer a fitness advantage in blood cells enabling them to outcompete. CH increases with age and has been linked to greater risk of hematologic cancer and cardiovascular disease.

Studies report increased prevalence of certain CH mutations with radio/chemotherapy and exposures such as smoking, thereby potentiating the risks of CH. Few efforts have aimed to broadly define associations between therapeutic exposures and CH.

Here, we connected real-world therapeutic exposure data to CH mutation data from >30,000 peripheral blood samples paired with matched solid tumor biopsies across cancer types.

METHODS

- De-identified records of patients sequenced with the Tempus xT solid tumor assay were selected from the Tempus Database (N=32,000).
- Across 30 solid tumor diagnoses, most were breast, pancreatic, prostate, ovarian, bladder, colon, and non-small cell lung cancer.
- Analysis was constrained to reported CH and myelodysplastic syndrome/acute myeloid leukemia-associated genes.
- >10,000 therapeutic exposures were recorded and categorized into 84 treatment classes. CH mutations were classified into distinct categories including:
  - Age-related.
  - DTA (mutations in *DNMT3A*, *TET2*, and *ASXL1*).
  - DNA damage response (DDR).
  - spliceosome mutations.
- Therapeutic exposures that were informative of each CH category were selected as features.
- Penalized likelihood logistic regression was used to quantify and test for significant associations between CH mutations and therapeutic exposures adjusting for covariates.

SUMMARY

Through an evaluation of real-world evidence, we revealed novel associations between functional CH categories and therapeutic exposures, especially among highly clonal DTA mutations. These findings provide a basis for using multimodal data to develop predictive models of CH modulation and progression to hematologic disease, which can be crucial in weighing the relative risks of therapeutic interventions in some patients with solid tumors.

RESULTS

CH Prevalence is Associated with Age and Varies by Cancer Type

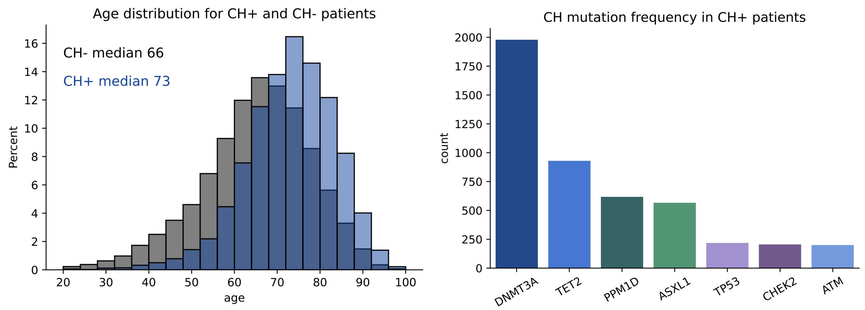

Figure 1. CH mutations were strongly age-associated (P < 0.001). When adjusting for age and sex, the frequencies of CH were highest in meningioma, endocrine tumors, lung cancer, and ovarian cancer. The most frequently mutated genes were *DNMT3A*, *TET2*, PPM1D, *ASXL1*,and *TP53.*

CH DTA Mutations Associated with Therapeutic Exposures

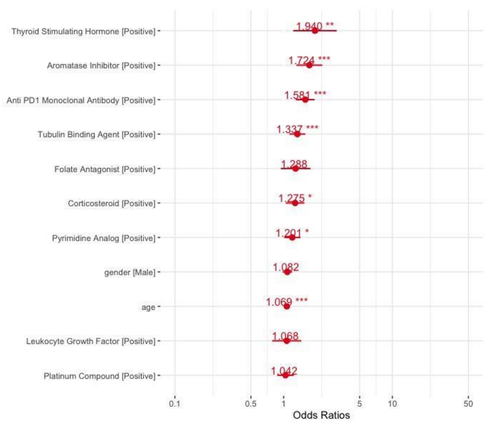

Figure 2. Highly clonal DTA mutations (variant allele fraction > 10%) were significantly increased with thyroid hormone replacement (P < 0.01) and aromatase inhibitor therapy (P < 0.001) accounting for menopause status. Significant upticks in the odds of DTA mutations were also noted for pyrimidine analogs, tubulin binding agents, and immunotherapy.

CH DDR Mutations Associated with Therapeutic Exposures

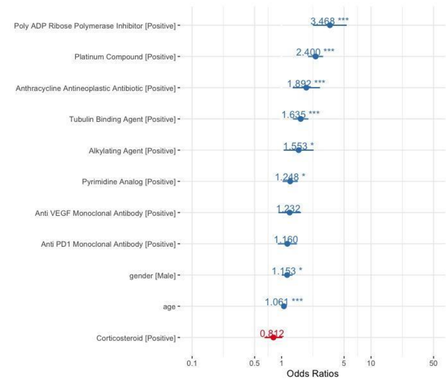

Figure 3. DDR mutations were most strongly associated with PARPi therapy, platinum agents, and anthracyclines (P < 0.001 for each). Lower magnitude associations with DDR mutations were noted for alkylating agents, pyrimidine analogs, and tubulin binding agents.

CH Spliceosome and *IDH1/2* Mutations Associated with Therapeutic Exposures

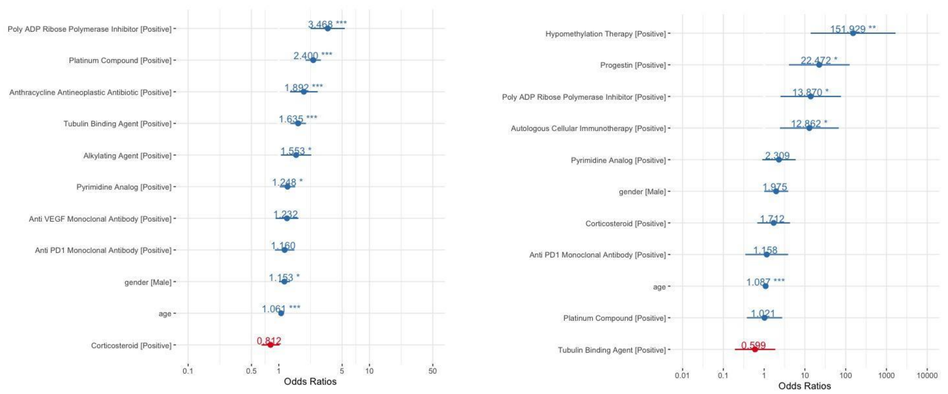

Figure 4. Spliceosome (4A) and *IDH1/2* (4B) mutations were most strongly associated with treatments for myeloid/lymphoid neoplasms. Intriguingly, a novel association was revealed between *IDH1/2* mutations and progestin (P = 0.013).

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