Abstract #3620

Genetic ancestry differences in tumor mutation and expression in early and average onset colorectal cancer

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INTRODUCTION

- The incidence and mortality of early onset colorectal cancer (EOCRC), defined as CRC[1] diagnosed prior to age 50, are rising. In contrast, incidence and mortality rates of average onset CRC (AOCRC) are declining.[2]
- **Epidemiologic trends for CRC appear to differ by race/ethnicity**, which could be associated with underlying differences in tumor mutation and gene expression.
- Previous research has used self-reported race/ethnicity categories, which has been shown to be missing or inaccurate, particularly in highly admixed groups such as Black and Hispanic.
- We examined tumor profiles of EOCRC and AOCRC using **global genetic ancestry proportions.**

METHODS

Cohort selection

- Overall: de-identified data of EOCRC (n=1,643) and AOCRC (n=3,175) patients who underwent tumor profiling with the Tempus xT NGS 648-gene panel and targeted RNAseq.
- Of these patients, 1,042 EOCRC and 1,850 AOCRC had **matched germline tissue** to ensure germline variants not misclassified as somatic.

Ancestry inference

- Ancestry informative markers were used to estimate likelihoods for the **five continental groups** defined in the 1000 Genomes Project[3]: Africa (AFR), Americas (AMR), East Asia (EAS), Europe (EUR), and South Asia (SAS).
- We have previously shown[4] that a heuristic method combining global ancestry proportions can impute race and ethnicity categories.

Statistical analysis

- Logistic regression was used to discover associations between genetic ancestry proportions (per **20% increase** in each ancestry proportion) with presence of protein altering somatic mutations in key driver genes in CRC:
  APC, BRAF, BRCA1, BRCA2, CDH1, EGFR, ERBB2, FBXW7, KRAS, MLH1, MSH2, MSH6, MUTYH, NRAS, NTRK1, NTRK2, NTRK3, PIK3CA, PMS2, PTEN, SMAD4, TP53
- Differences in association by onset age (EOCRC vs. AOCRC) were determined by adding interaction terms to regression models.
- We considered SNVs, small indels, and CNVs, and used data only from patients with paired tumor/normal sequencing.

SUMMARY & DISCUSSION

- We confirm several **ancestry-dependent associations** with somatic mutations in *KRAS*, *APC*, and *BRAF*.
- The association between African ancestry and mutations in *APC* was observed only in AOCRC.
- We observe **novel associations** between somatic mutations in *TP53* and *MLH1* and Asian and Amerindian ancestries, respectively.

RESULTS

Figure 1. Distribution of ancestry proportions for the patients in our cohort

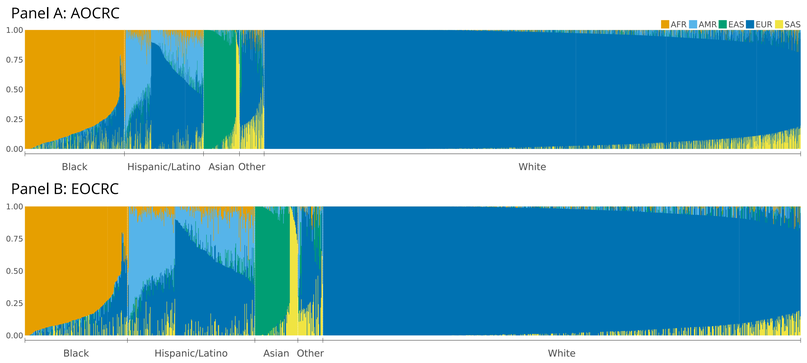


Fig 1. shows the distribution of ancestry proportions for subjects in both the AOCRC (Panel A; n=3,175) and EOCRC (Panel B; n=1,643) subgroups – each vertical line is a subject and the colors correspond to the estimated global continental ancestry proportions as per color codes indicated in the legend. Patients have been grouped by their imputed race/ethnicity category derived from ancestry proportions (see methods). While we find similar numbers of Black and Asian patients in both groups (13% and 5-6%), we find more Hispanic/Latino patients in the EOCRC subgroup (increase from 10% to 16%).

Figure 3. Ancestry associations for somatic mutations in *APC* stratified by early or average onset

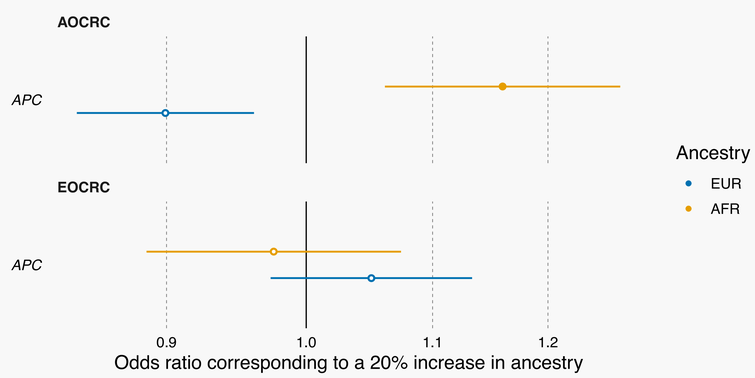
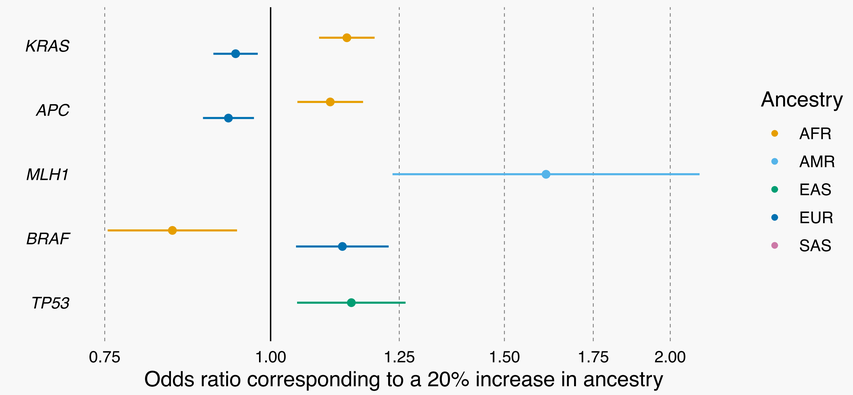


Figure 2. Ancestry associations with somatic mutations in CRC genes



- Across all ages, African ancestry was associated with higher odds of somatic mutations in *APC* (OR=1.11) and *KRAS* (OR=1.14) and lower odds of *BRAF* mutations (OR=0.84).
- East Asian ancestry was associated with higher odds of mutations in *TP53* (OR=1.15).
- Amerindian ancestry with higher odds of somatic mutations in the *MLH1* gene (OR=1.61). Notably, this analysis considers only patients where paired tumor normal sequencing was performed, and thus cannot be explained by germline variants in this DNA repair gene (*i.e.* Lynch syndrome).
- When stratified by age, for AOCRC, the association between *APC* and African ancestry was observed (OR 1.16, p=0.001), whereas it was not observed for EOCRC (OR=0.98, p=0.617), *p* interaction = 0.003 (Fig 3).

References: [1]Siegel *et al.,* J Natl Cancer Inst. 2017;109(8):1974–2013.; [2]Holowatyj *et al.*, ClinOncol. 2016;34(18):2148–2156; [3]1000 Genomes Project Consortium, Nature. (2015) Oct 1;526(7571):68-74; [4]Hein *et al.,* J Natl Cancer Inst (2022) Feb 2; djac014. doi: 10.1093/jnci/djac014.

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