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

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INTRODUCTION

- The incidence and mortality of early onset colorectal cancer (EOCRC), defined as CRC diagnosed prior to age 50, are rising. In contrast, incidence and mortality rates of average onset CRC (AOCRC) are declining.
- **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=1,792) and AOCRC (n=5,221) patients who underwent tumor profiling with the Tempus xT NGS 648-gene panel and targeted RNAseq.
- Of these patients, 1,139 EOCRC and 3,185 AOCRC had **matched germline tissue** to ensure germline variants were 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 Africa (AFR), Americas (AMR), East Asia (EAS), Europe (EUR), and South Asia (SAS).
- Race/ethnicity categories were imputed using admixture thresholds based on literature and comparisons with available stated race/ethnicity data

Statistical analyses

- Ancestry proportions were transformed into isometric logratio pivot coordinates, then used as predictors in logistic regression models to discover associations between genetic ancestry proportions and the presence of somatic mutations. **Each ancestry proportion association is thus adjusted for every other ancestry.**
- 137 cancer pathway and predicted CRC driver candidate genes were tested.
- Differences in association by onset age (EOCRC vs. AOCRC) were determined by adding interaction terms to regression models.
- We considered SNVs and small indels and used data only from patients with paired tumor/normal sequencing.

SIGNIFICANCE

- We confirm African **ancestry associations with somatic mutations** in *APC* and *KRAS*.
- We observe **novel associations** between somatic mutations in *ARID1B* and East Asian ancestry and *MLH1* and *NOTCH3* and Amerindian ancestry.
- Associations of African ancestry with *APC* somatic mutations and European ancestry with *RNF43* somatic mutations **differ by onset age**.

RESULTS

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

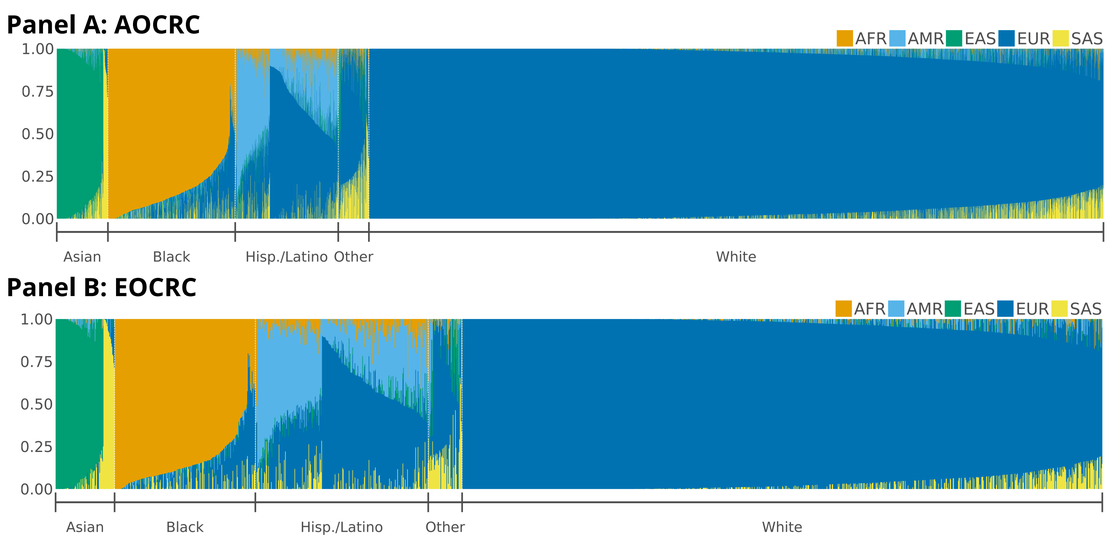

Fig. 1 shows similar proportions of Asian and Black patients were observed in both EO and AO groups (5-6% and 12-13%); however, a larger share of Hispanic/Latino patients was found in the EO subgroup (17%) compared to AO (10%).

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=1.05) and *KRAS* (OR=1.04).
- East Asian ancestry had lower odds of mutations in *ARID1B* (OR=0.91).
- Amerindian ancestry had higher odds of somatic mutations in *NOTCH3* (OR=1.09) and *MLH1* (OR=1.15). Notably, all patients underwent paired tumor normal sequencing, so this result cannot be explained by germline variants in this DNA repair gene (*i.e.* Lynch syndrome).

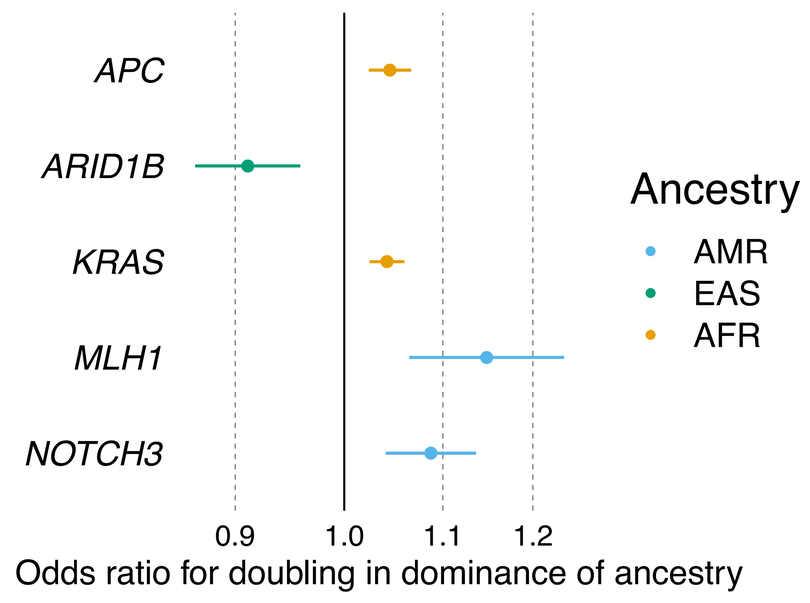

Figure 3. Associations by onset age

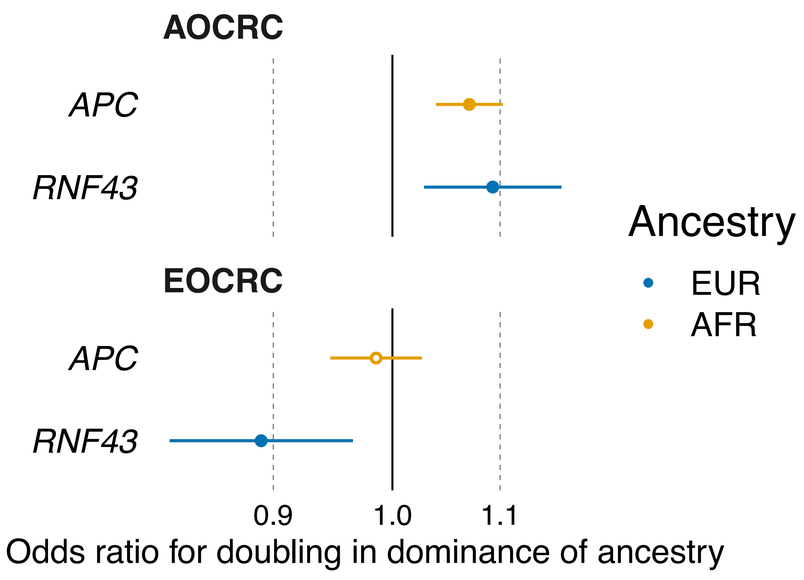

Fig. 3 shows that the association between *APC* and African ancestry is present only in AOCRC (OR=1.07, p=6.6x10^{-6}), and absent in EOCRC (OR=0.99, p=0.49). A positive association of European ancestry and *RNF43* mutations was observed in AOCRC (OR=1.09), but the association was negative in EOCRC (OR=0.89), p interaction = 4.3x10^{-5}.

Acknowledgements: We thank Vanessa Nepomuceno, Ph.D., from Tempus Scientific Communications for editorial poster review
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