Genetic Ancestry Associations with Pancreatic Cancer Mutational Profiles from a Diverse 9,274-Patient Real-World Cohort

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INTRODUCTION

Pancreatic cancer is an aggressive malignancy associated with racial and ethnic disparities. Black patients have a higher incidence and mortality compared to their White counterparts. However, low representation of Black and Hispanic patients in cancer genomics studies hampers our understanding of genomic factors contributing to differential outcomes. Furthermore, comparisons between racial groups fail to capture differences in genetic ancestry.

We studied associations between genetic ancestry and imputed race and ethnicity categories with pancreatic mutational profiles using a large, diverse real-world cohort.

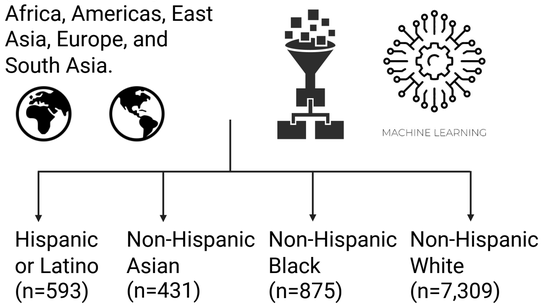
METHODS

9,274 patients with pancreatic cancer

654 ancestry-informative markers used to estimate genetic ancestry for Africa, Americas, East Asia, Europe, and South Asia.

Molecular profiling with Tempus xT 648-gene NGS test between 2018-2022

Race and ethnicity categories imputed from a previously published machine learning model.[1]



Associations between either race and ethnicity category or genetic ancestry proportions and somatic variants--copy number alterations (CNAs), small nonsynonymous mutations, OncoKB L1/2 & R1, and predicted driver somatic mutations using boostDM[2]--were assessed for 172 pancreatic cancer-related genes as well as gene sets using logistic regression models.

Models with and without imputed race and ethnicity or genetic ancestry terms were compared with likelihood ratio (LR) tests, and p-values were adjusted to control the FDR at 5%. Associations of imputed race and ethnicity category with TMB were tested with Kruskal-Wallis rank sum tests. Tests of TMB and small variants used patients with available matched normal tissue only to avoid artifacts from misclassification of germline variants.

SUMMARY

• Among pancreatic cancer patients, having either a CNA or small nonsynonymous mutation in any of four receptor tyrosine kinase (RTK) genes was associated with genetic ancestry.

• These results are modest, suggesting that there are not large differences in mutational profiles for pancreatic cancer according to genetic ancestry or by race and ethnicity.

RESULTS

Mutation types and genes tested

Mutation type	Samples included	N tests	Genes tested
Small, nonsynonymous	Tumor normal matched	32	*ACVR1B, ALK, APC, ARID1A, ARID1B, ARID2, ATM, BRAF, BRCA2, CDKN2A, CIC, CTNNB1, ERBB4, FLT4, GNAS, IRS2, KDM6A, KRAS, NF1, NOTCH1, NOTCH3, PBRM1, PIK3CA, PREX2, RB1, RET, SMAD3, SMAD4, SMARCA4, STK11, TGFBR2, TP53*
Copy number alterations	All samples	8	*AKT2, CCNE1, CDKN2A, CDKN2B, GATA6, MCL1, MYC, SMAD4*
OncoKB therapeutic level L1, L2, or resistance level R1	All samples	2	*KRAS, PIK3CA*
Predicted driver somatic mutations using boostDM	Tumor normal matched	5	*ARID1A, CDKN2A, KRAS, SMAD4, TP53*
Small, nonsynonymous mutations or CNAs in gene sets populated from literature review	Tumor normal matched	4	1. RAS/RAF/MEK/ERK pathway: *KRAS, RAF1, ARAF, BRAF, MAP2K1, MAPK* 2. Chromatin remodeling complexes: *ARID1A, ARID1B, SMARCA4, PBRM1* 3. DNA damage remodeling gene: *BRCA1, BRCA2, PALB2, ATM, MLH1, MSH2, MSH6* 4. Receptor tyrosine kinases: *ERBB2, EGFR, MET, FGFR1*

Table 1. Mutation types, sample types, number of tests, and genes and gene sets tested. Only genes and gene sets with mutations present in at least 1% of patients were tested. To increase statistical power, mutation types were combined and genes were grouped into gene sets.

CNA or small nonsynonymous mutation in the RTK gene set is associated with genetic ancestry

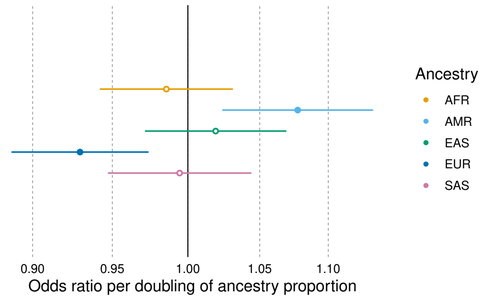


Figure 1. Genetic ancestry associations with RTK genes. Among pancreatic cancer patients, having either a CNA or small nonsynonymous mutation in an RTK gene was positively associated with AMR and negatively associated with EUR ancestry. Odds ratios represent the change in odds of a somatic mutation for every doubling of a specific ancestry proportion, adjusted for assay version, gender, and the other four ancestry proportions. Filled circles indicate p<0.05, open circles indicate p≥0.05.

Imputed race and ethnicity category was non-significantly associated with RTK changes

Patient group	N total	N with mutation	LR test p-value	LR test p-value corrected for 4 tests	Ancestry or imputed race and ethnicity	OR (95% CI)	Logistic p-value
Genetic ancestry results							
All pancreatic cancer	4,944	197	0.007	**0.027**	AMR	1.08 (1.02-1.13)	0.004
					EUR	0.93 (0.89-0.97)	0.002
Ductal adenocarcinoma	4,351	172	0.066	0.264	AMR	1.07 (1.01-1.13)	0.022
					EUR	0.94 (0.89-0.99)	0.011
Imputed race and ethnicity results							
All pancreatic cancer	4,904	196	0.022	0.080	NH Asian	1.92 (1.10-3.32)	0.021
					Hispanic or Latino	1.79 (1.13-2.85)	0.014
Ductal adenocarcinoma	4,498	172	0.039	0.157	NH Asian	1.79 (0.97-3.30)	0.061
					Hispanic or Latino	1.87 (1.15-3.04)	0.012

Table 2. Genetic ancestry and imputed race and ethnicity category associations with RTK genes. Tests were performed in all pancreatic cancer patients and restricted to only those with ductal adenocarcinoma. Odds ratios for genetic ancestry are for every doubling of a specific ancestry proportion, adjusted for assay version, gender, and the other four ancestry proportions. Odds ratios for imputed race and ethnicity are with respect to the NH White group and are adjusted for assay version and gender.

Imputed race and ethnicity group is not associated with TMB

	Hispanic or Latino	NH Asian	NH Black	NH White	No Call	Kruskal-Wallis p-value
Patients with tumor tissue only						
N	254	212	389	3,444	26	
Median TMB (mutations/mb)	3.43	3.87	4.23	3.07	3.07	<2.2e-16
Patients with matched normal tissue						
N	339	219	486	3,865	40	
Median TMB (mutations/mb)	1.54	1.54	1.90	1.67	1.78	0.2

Table 3. Count of patients and median TMB by imputed race and ethnicity category, stratified by availability of matched normal tissue. Imputed race and ethnicity category is not associated with TMB in patients with matched normal samples.

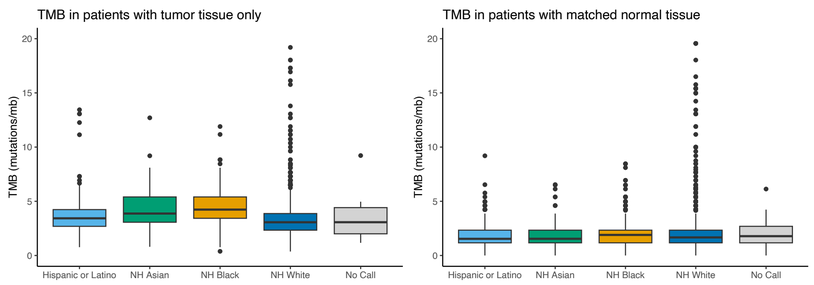


Figure 2. TMB by race and ethnicity category stratified by availability of matched normal tissue samples. TMB measures are known to be inflated in populations of non-EUR genetic ancestry when matched normal tissue is unavailable for calling somatic variants due to reliance on reference population databases dominated by EUR genetic ancestry.[3] Plot is trimmed at 20 mutations/mb.

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