#3087: Influence of genetic ancestry on UV mutational signatures linked to immunotherapy response in melanoma, beyond TMB

Magnaye KM[1], Gilg B[1], Dickman LR[1], Spies N[1], Plagens RN[1], Samec TM[1], Farrell A[1], Gobran B[1], Ramkumar K[1], Zheng M[1], Wu X[1], De Niz C[1], Wan E[1], Deacon DC[2], Montoya DJ[3], Brownell I[4], Fejerman L[3], Carvajal-Carmona LG[3], Mitsiades N[3], Lott P[3], Holmen SL[2], Shalhout SZ[5], Ghani H[1], Helmstetter A[1], Elliott A[1], Klemp J[1], Stransky N[1], Xiu J[1], Yang YJ[1], Radovich M[1], Oberley MJ[1], Hamrick J[1], Spetzler D[1], Sledge GW[1], Raj SM[6], Abdulla F[1]

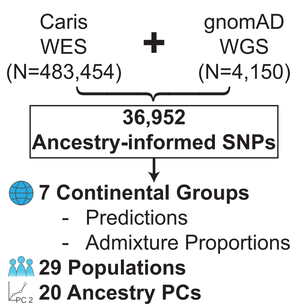
[1]Caris Life Sciences, Phoenix, AZ; [2]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [3]Comprehensive Cancer Center, University of California, Davis, Davis, CA; [4]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD; [5]Department of Otolaryngology-Head and Neck Surgery, Mass Eye and Ear, Harvard Medical School, Harvard University, Boston, MA; [6]Department of Genetics, Albert Einstein College of Medicine, New York City, NY

Background

- Melanoma is driven by UV-induced mutagenesis, yet immunotherapy response remains incompletely explained by tumor mutational burden (TMB) alone.
- Underrepresentation of non-European populations in genomic studies limits understanding of ancestry-associated differences in melanoma biology and biomarker performance.
- Using >483,000 tumor-only WES samples, we evaluated how genetic ancestry and UV mutational signatures stratify melanoma biology and immunotherapy outcomes.

UV-associated mutational processes differ across genetic ancestry groups and identify melanoma patients more likely to benefit from immune checkpoint inhibitor therapy

Caris Genetic Ancestry Platform



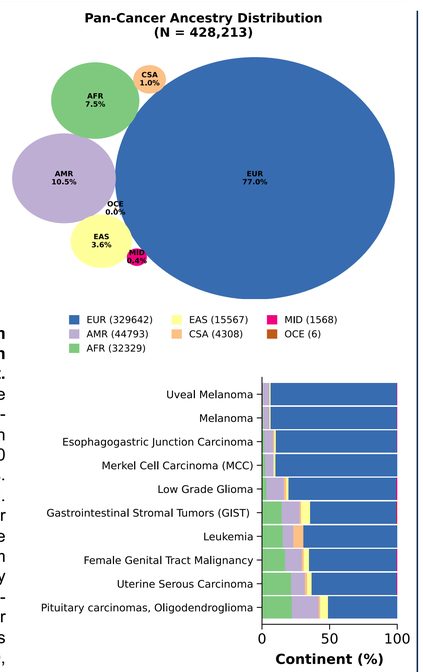


Figure 1. Genetic ancestry inference from exome sequencing reveals population diversity across a pan-cancer cohort. (**Top left**) Overview of the ancestry inference pipeline integrating 36,952 ancestry-informative variants from tumor-only WES with a machine-learning classifier trained on 4,150 globally diverse gnomAD reference genomes. A total of 483,454 exomes were analyzed. (**Top right**) Continental ancestry distribution for the 428,213 cases receiving high-confidence ancestry assignments for downstream analyses. (**Right**) Continental ancestry fractions across the five most European-enriched and five most African-enriched tumor lineages. EUR, European; AMR, Indigenous American; AFR, African; EAS, East Asian; MID, Middle Eastern; CSA, Central/South Asian.

Results

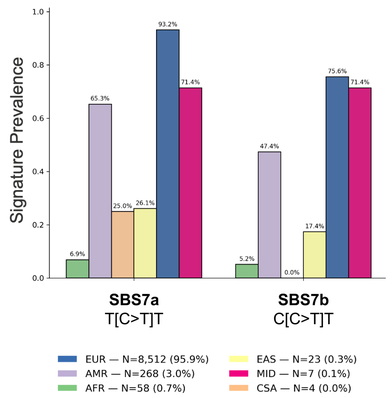
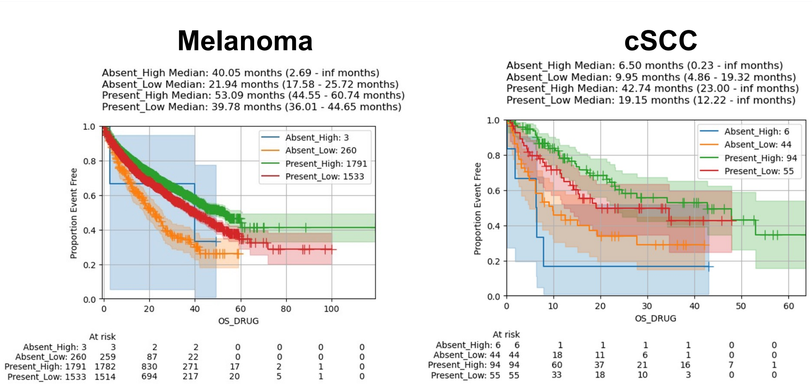


Figure 2. UVB-associated COSMIC signatures differ across genetic ancestry groups. Using tumor-only WES data, we detected the UVB-associated mutational signatures SBS7a and SBS7b linked to ultraviolet-induced DNA damage. SBS7a/b prevalence significantly differed across continental ancestry groups (Kruskal-Wallis p<0.05), with enrichment in melanomas from patients of European ancestry (93.2% and 75.6%, respectively) and low prevalence in patients of African ancestry (6.9% and 5.2%, respectively).



Comparisons	HR (95% CI)
SBS7a+ TMB-H vs SBS7a+ TMB-L	**0.80 (0.71-0.90)**
SBS7a+ TMB-H vs SBS7a- TMB-L	**0.49 (0.41-0.60)**
SBS7a+ TMB-L vs SBS7a- TMB-L	**0.62 (0.51-0.74)**

Comparisons	HR (95% CI)
SBS7a+ TMB-H vs SBS7a+ TMB-L	0.67 (0.40-1.13)
SBS7a+ TMB-H vs SBS7a- TMB-L	**0.37 (0.22-0.62)**
SBS7a+ TMB-L vs SBS7a- TMB-L	**0.58 (0.34-0.99)**

Figure 3. SBS7a identifies ICI benefit in TMB-low patients across cutaneous malignancies. Kaplan-Meier analysis of overall survival (OS) following first-line immune checkpoint inhibitor (ICI) therapy in cutaneous melanoma and cutaneous squamous cell carcinoma (cSCC), stratified by SBS7a status (Present vs. Absent) and tumor mutational burden (TMB-high vs. TMB-low). TMB cutoffs were defined using cohort median values (14.8 and 36.7 mutations/Mb, respectively). SBS7a identified favorable-outcome TMB-low patients not captured by TMB alone. In multivariable Cox analysis of cutaneous melanoma adjusting for TMB, age, sex, and ancestry principal components, SBS7a remained independently associated with improved OS (p=0.043). Bolded HR values indicate statistically significant associations (p<0.05).

Conclusions

- Using tumor-only WES from >483,000 patients, we developed a scalable framework for ancestry-aware precision oncology analyses.
- UVB mutational signatures (SBS7a/b) were enriched in melanomas from patients of European ancestry and rare in melanomas from patients of African ancestry.
- SBS7a was associated with improved immunotherapy outcomes beyond TMB, identifying favorable-outcome TMB-low melanoma patients not captured by TMB alone.

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