Molecular pathology selected abstracts

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African heritage tumor sequencing: variation in mutational changes among prevalent cancer types

February 2024—Precision cancer medicine relies heavily on understanding the genomic landscape of tumors. Prior comparisons between African and European ancestry, though based on limited data, have indicated distinct differences in the landscape of cancer driver alterations between these populations. Whether these discrepancies are mediated by genetic variants or environmental influences is still unclear. Accurately characterizing ancestry-associated genomic alterations is essential to not only improving genomic diagnostic testing but also to developing targeted therapies, biomarkers, and personalized cancer care for diverse populations. The authors conducted a study that leveraged two large genomic cohorts to investigate the relationship between genomic alterations and African ancestry in six common cancers: prostate, pancreas, ovary, nonsmall cell lung cancer (NSCLC), colorectal, and breast. The study used 333,908 tumor-only samples as the discovery cohort and 64,173 paired tumor-normal samples as the validation cohort. The authors found that continental and subcontinental ancestry can be inferred from targeted gene panel sequencing of tumor-only DNA. African ancestry was identified in 9.8 percent of all samples in the discovery cohort. The sequenced cohort had a distribution across cancer types that closely mirrored patterns observed in the general population. The authors associated the percentage of African ancestry per individual with 253 cancer genes, using a logistic regression model adjusted for the presence or absence of an oncogenic alteration in the gene, while accounting for age, gender, tumor mutational burden, subtype, and panel version. Some associations were replicated in multiple tumor types. For example, *MYC* amplifications were associated with African ancestry in NSCLC, prostate cancer, and breast cancer. They were also associated with worse overall survival for each cancer type. In examining the prevalence of oncogenic drivers in NSCLC, the authors found that patients of African ancestry who did not exhibit the mutational signature associated with smoking had a greater occurrence of *ROS1* fusions. African heritage was also found to be linked to a reduced occurrence of *KRAS* mutations, irrespective of smoking habits. Furthermore, driver mutations in *TP53* were only associated with smoking. This implies that the effects of smoking on the body may differ in people of African descent. Another aspect of the study assessed biomarkers used to guide therapeutic decisions in patients of African ancestry, such as tumor mutational burden (TMB) and microsatellite instability (MSI) status for immune checkpoint inhibitors and homologous recombination repair (HRR) deficiency for poly-ADP ribose polymerase inhibitors. The results showed that TMB-high status was more common in patients of African ancestry who had NSCLC and prostate cancer and that colorectal cancer patients had a lower frequency of mutations in HRR genes and mismatch repair genes and of MSI-high status. The study findings underscore the importance of ensuring equal access to diagnostic testing and precision oncology to address disparities in cancer care. The authors stressed the need to incorporate a wide range of patient populations in future studies to gain a deeper understanding of how ancestry and environmental factors interact with tumor biology.

Jiagge E, Jin DX, Newberg JY, et al. Tumor sequencing of African ancestry reveals differences in clinically relevant alterations across common cancers. *Cancer Cell*. 2023;41:1963–1971.

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Molecular association between VEXAS syndrome and clonal hematopoiesis

VEXAS syndrome is characterized by widespread inflammation throughout the body. It is caused by somatic mutations in the *UBA1* gene (*UBA1*^{mut}), which is located on the X chromosome. The mutations are passed down in the myeloid lineage and activate inflammatory pathways, leading to severe systemic inflammatory symptoms. Those diagnosed with VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome are more likely to develop hematologic malignancies, such as myelodysplastic syndrome and plasma cell dyscrasias. Clonal hematopoiesis is a common age-related phenomenon characterized by the expansion of hematopoietic stem and progenitor cells harboring somatic mutations. The frequency and medical significance of concurrent clonal hematopoiesis mutations and *UBA1* mutations in VEXAS have yet to be determined. The authors conducted a study to define the clonal hematopoiesis landscape and how it affects patients with VEXAS syndrome, using error-corrected and single-cell DNA sequencing, and correlated these findings with clinical outcomes. They retrospectively screened 80 patients with VEXAS for clonal hematopoiesis mutations. Sixty percent of patients had typical myeloid mutations that co-occurred with the *UBA1* mutations associated with VEXAS. Furthermore, approximately half of the patients exhibited somatic mutations in two or more myeloid genes, which suggests that these people have a higher likelihood of developing mutant clones. The mutations primarily consisted of *DNMT3A* and *TET2* and were detectable in about 50 percent of patients. However, the authors also observed somatic mutations in traditional myelodysplastic syndrome-associated genes, such as *TP53, KRAS, NRAS, SF3B1, STAG2,* and *IDH2*. The variant allele frequencies for *UBA1* mutations consistently indicated that *UBA1* was the dominant clone in hematopoiesis. The mean variant allele frequencies for other mutant myeloid genes ranged from 27 percent for *DNMT3A* to less than 1.5 percent for *TET2*. Analysis of DNA at the single-cell level showed clear patterns of clonality. The mutations in *DNMT3A* occurred primarily before the *UBA1* mutation, indicating that the *UBA1* mutation occurred in the context of clonal hematopoiesis driven by *DNMT3A. TET2* and other genes predominantly manifested as *UBA1*-mutant subclones or separate clones. The study suggests that *DNMT3A* and *TET2* mutations may contribute to inflammation and propagate it in people with VEXAS. These clones, often found in conjunction with clonal hematopoiesis with *UBA1* mutations, promote inflammation and immune cell activation. This study establishes the foundation for a more comprehensive understanding of how *DNMT3A* and *TET2* mutations and other myeloid drivers play a role in *UBA1*-mutant clones developing into myeloid malignancy. The study supports *UBA1* causing myeloid clonal expansion and inflammatory and hematologic phenotypes in VEXAS.

Gutierrez-Rodrigues F, Kusne Y, Fernandez J, et al. Spectrum of clonal hematopoiesis in VEXAS syndrome. *Blood*. 2023;42(3):244–259.

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