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## Multi-ethnic study uncovers unique origins of melanoma types and actionable molecular targets

**Lyon, France, 21 July 2022** – Scientists from the International Agency for Research on Cancer (IARC), Barretos Cancer Hospital (Brazil), and partners have identified multi-omics markers of exposure to ultraviolet radiation (UV) that are critically involved in immune function, have the potential to drive cancer development, and could be used to predict the survival of patients with cutaneous melanoma, which occurs mainly in fair-skinned people. The study, published in *Nature Communications*,<sup>1</sup> also reveals important features of melanomas that are not associated with UV exposure; this opens a window of opportunity for new therapeutic targets for a less obvious population: patients with acral melanoma, which is the most common type of melanoma in darker-skinned people.

“We are revisiting archived clinical samples with modern technologies and computational tools to construct molecular maps of the patients’ DNA that help us to uncover genes that affect survival and to trace back the origins that drive melanoma development,” explains IARC scientist Dr Akram Ghantous, a co-author of the study. “By including patients with different skin colours, we widen the resolution spectrum to various forms of melanoma and gain a better understanding of those origins, which are not necessarily triggered by UV exposure. I hope our findings will provide clinicians with a molecular lens that helps them better see ‘through’ their patients’ skin and its various colours.”

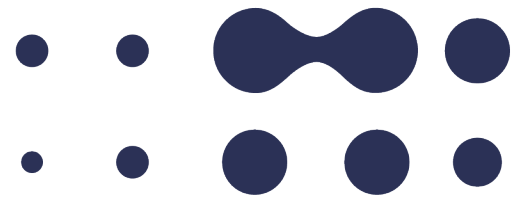
### Results

For cutaneous melanomas that did not occur as a result of UV exposure, the molecular landscape and clinical prognosis not only were different from those of UV-exposed melanomas but also resembled those of acral melanoma, a pathologically distinct type that develops in skin areas not often exposed to sunlight, such as the palms of the hands and the soles of the feet. These gene–environment interactions in people of different ethnic backgrounds reveal translationally impactful mechanisms in melanomagenesis.

“The interdisciplinary findings of this work can undoubtedly help us clinicians to view and analyse melanoma tumours from various angles,” says Dr Vinicius Vazquez, a physician at Barretos Cancer Hospital and a co-author of the study. “I’m excited by the opportunity to help implement these findings in the diagnosis and treatment of my patients with melanoma.”

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<sup>1</sup> Vicente ALSA, Novoloaca A, Cahais V, Awada Z, Cuenin C, Spitz N, et al. (2022). Cutaneous and acral melanoma cross-OMICs reveals prognostic cancer drivers associated with pathobiology and ultraviolet exposure. *Nat Commun*, Published online 15 July 2022; <https://doi.org/10.1038/s41467-022-31488-w>



UV exposure is causally linked to cutaneous melanoma, but the underlying epigenetic mechanisms, known as molecular sensors of exposure, have not been characterized in clinical biospecimens. In this study, the researchers used powerful DNA sequencing technologies to infer UV exposure based on mutational signatures and integrated clinical, epigenomic (DNA methylome), genomic, and transcriptomic data of cutaneous and acral melanomas from two multi-ethnic cohorts.

“I’ve learned a lot from the multiple disciplines of this research, including a critical and balanced interpretation of the findings,” says Ms Anna Luiza Vicente, a researcher at Barretos Cancer Hospital and a co-author of the study. “As an early-career woman in science, I felt empowered by such an interdisciplinary study and team of investigators, and I’m eager to continue my research journey on melanoma.”

The top marker identified in this work encompassed several UV-altered DNA methylation sites, which were validated by independent targeted sequencing, providing a cost-effective opportunity for clinical application.

“There is a growing interest in personalized approaches to the treatment and prevention of cancer (including melanoma), which take into account differences in the molecular architecture of individual tumours but also causes that are potentially preventable,” says Dr Zdenko Herceg, Head of the Epigenomics and Mechanisms Branch at IARC and a co-author of the study. “Therefore, investigating the epigenome has a tremendous impact on our understanding of the causes and the behaviour (phenotype) of cancer and on developing novel strategies for cancer treatment and prevention.”

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