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Shining a light on melanomas that aren't caused by the sun

'Slip, slop, slap' is synonymous with being Australian and playing it safe in the sun. These sun smart rules reduce our chances of getting melanoma of the skin. However, new research tells a different story for those affected by rarer forms of melanoma.

The genetic study, led by Australian researchers at Melanoma Institute Australia, QIMR Berghofer Medical Research Institute and The University of Sydney as part of the Australian Melanoma Genome Project, has found that melanomas on the hands and feet (known as acral) and internal surfaces (known as mucosal) are not linked to ultraviolet (UV) radiation. This is in contrast to melanoma of the skin, which is strongly related to UV radiation.

The research, published today in the prestigious *Nature* journal, shows that acral and mucosal melanoma have different causes to skin melanoma. This has implications for preventing and treating these forms of melanoma, which occur worldwide.

"This is by far the largest study to have looked at the whole genome in melanoma, and it has proven these less common melanomas are strikingly different in terms of their causes," says Professor Richard Scolyer, Conjoint Medical Director of Melanoma Institute Australia and a lead author.

Every year in Australia, up to 420 people are diagnosed with acral or mucosal melanomas. They affect people of all ethnic backgrounds, and are the most common forms of melanoma in people with very dark skin. These forms of melanoma often behave more aggressively, are harder to diagnose and have a poorer outcome compared to skin melanoma.

Treatment for skin melanoma has advanced rapidly in recent years, with therapies tripling the life expectancy of some advanced melanoma patients. For the first time, this research sheds light on why revolutionary treatments—many of which have been pioneered at Melanoma Institute Australia—don't work as well for acral or mucosal melanomas.

"Acral and mucosal melanomas occur all over the world, but they have been even more challenging to treat than skin melanoma," says Professor Nicholas Hayward, a lead author from QIMR Berghofer Medical Research Institute. "Knowing these are really different diseases to skin melanoma is important for development of future therapies."

The study also found acral and mucosal melanomas have much less gene damage compared with skin melanoma and the damage "footprints" did not match those of any known causes of cancer, like sun exposure. This means we must target new research to discover what is causing these cancers, and what can prevent them.

While they had fewer gene drivers that could be targeted for therapy, new ones were found. Some mucosal melanomas unexpectedly had mutations in the SF3B1 and GNAQ genes, which had previously only been connected to melanoma of the eye.

Understanding which gene mutations are driving an individual tumour is the basis of personalised cancer medicine. This is the first study to survey the entire DNA sequence of melanomas, not just the genes themselves, giving 50 times more information than in previous work. Many genes were found to have damage in their control regions, the so-called "dark matter" of our genome, and these may be previously unsuspected drivers of melanoma.

"This is a world-leading genetic analysis of melanoma," explains Professor Graham Mann, a lead author at Melanoma Institute Australia. "We are working hard now to turn these discoveries about the uniqueness of acral and mucosal melanoma, and about the new control mutations, into better results for our melanoma patients."

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Background on melanoma

Melanoma is the most deadly of all skin cancers. Almost 14,000 Australians are expected to be diagnosed with melanoma in 2017; 2-3% of them will be diagnosed with acral and mucosal melanoma. The incidence of acral and mucosal melanoma is equal among different races, but it is the most common melanoma subtype in dark-skinned populations due to the rarity of skin melanoma.
Acral melanoma occurs on the soles of the feet, palms and nails (most commonly on the feet).
Mucosal melanoma occurs in mucous membrane lining the respiratory, gastrointestinal and urogenital tract. Most mucosal melanomas originate in the nasal cavity and sinuses, oral cavity, anorectum, vulva and vagina.

Acral and mucosal melanomas are often diagnosed at an advanced stage as they are harder to detect. Treatment options are often less effective than for other forms of skin melanoma, so prognosis is often poor.

Background on the Australian Melanoma Genome Project

The research was undertaken as part of the Australian Melanoma Genome Project—the largest melanoma research effort ever undertaken in Australia with a national coalition of researchers from Melanoma Institute Australia, QIMR Berghofer Medical Research Institute, The University of Sydney, Royal Prince Alfred Hospital, The Westmead Institute for Medical Research, Peter MacCallum Cancer Centre, The Olivia Newton-John Cancer Research Institute and Bioplatforms Australia working together. Launched in 2012, the project seeks to change how melanoma is diagnosed and treated by identifying the common genetic mutations that drive melanoma, and that can be targeted in personalised treatment.

The Australian Melanoma Genome Project was funded by Melanoma Institute Australia, the NSW Ministry of Health, Cancer Council NSW and the Australian Government through Bioplatforms Australia.