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**QIMR Berghofer**  
Medical Research Institute

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## **Australian researchers use whole genome sequencing to find unexpected genomic landscape in melanoma**

By looking at the 'dark matter' of the genome, a new study published today in *Nature* has found that genetic changes in melanomas on the hands and feet (acral) and internal surfaces (mucosal) are completely different to the mutations found in skin melanoma. This confirms them as very distinct diseases from each other.

Researchers at Melanoma Institute Australia, QIMR Berghofer Medical Research Institute and The University of Sydney led the study – the largest gene-sequencing study ever undertaken in melanoma, and one of the biggest in the field of oncology – as part of the Australian Melanoma Genome Project.

“Our study has provided a whole series of observations and important new insights from whole genome sequencing, some of which you would expect but others which are quite surprising,” said Professor Richard Scolyer, Conjoint Medical Director of Melanoma Institute Australia and a lead author. “These findings will change the future direction of melanoma research and open the door to develop more effective treatments for patients with acral and mucosal melanoma.”

This is the first large study to survey the entire DNA sequence of melanomas, giving 50 times more information than most previous work which has focussed on the coding regions of genes. Many genes were found to have damaged control mechanisms and may be previously unsuspected drivers of melanoma.

Ground-breaking knowledge of melanoma identified from this study includes:

### **UV radiation does not cause acral or mucosal melanoma**

Utilising whole-genome sequencing on tumours from 183 patients, the study found genetic mutations caused by ultraviolet (UV) radiation was dominant in skin melanoma, whereas complex structural rearrangements **not caused** by UV radiation dominated in acral and mucosal melanoma. In fact, none of the other known genetic signatures for environmental causes of cancer matched with what was seen in acral and mucosal melanoma.

“No ‘smoking gun’ was found for the cause of acral and mucosal melanoma, and this means we still need to keep looking,” said Professor Nicholas Hayward, a lead author from QIMR Berghofer Medical Research Institute. “We know that sun protection works to prevent skin melanoma, but it’s not going to get these other forms of melanoma under control.”

These findings show that not only do acral and mucosal melanoma have different causes to skin melanoma, but they explain why new therapies that have been so successful in treating skin melanoma have been less unsuccessful in treating acral and mucosal melanoma.

### **New driver mutations were identified in skin melanoma**

By studying the whole genome, researchers have identified a number of new uncommon driver mutations in skin melanoma and confirmed the importance of other major mutations driving melanoma.

“We did not see any melanoma driver mutations that were as common as the ones we already knew about, such as BRAF. This is an important negative finding,” commented Professor Graham Mann, a lead author at Melanoma Institute Australia. “However, we have shown for the first time that melanomas carry a wide range of mutations in gene control mechanisms, and some of these are very likely to be drivers.”

“We overcame important technical difficulties to find this out. Skin melanoma is riddled with mutations because the sun is so effective at damaging genes. That creates a lot of noise and makes it challenging to *find the wood for the trees.*”

The researchers engaged a team, led by Professor Núria López-Bigas from the Institute for Research in Biomedicine and Pompeu Fabra University, Barcelona, which is expert in separating this genomic noise. They applied a new technique to the melanoma genome data to correctly identify which mutations are most important, and therefore which genes are the most promising targets for therapy.

### **Mucosal melanoma is genetically similar to eye melanoma**

Although there are fewer genetic mutations in mucosal melanoma compared to skin melanoma, the research identified specific driver mutations (SF3B1 and GNAQ genes) that are similar to those found in eye (uveal) melanoma. This could have important outcomes for therapeutic development and helps explain why treatments that often work in skin melanoma are often ineffective in uveal, acral and mucosal melanoma.

### **Advances in unravelling our understanding of telomeres**

A paradoxical relationship between mutations to the telomerase enzyme and telomere length was observed, which may help unravel our understanding of the relationship of these mutations in tumour development.

Cells that have to live a long time have to be able to continuously repair and maintain their telomeres. A key genetic mutation previously observed in most melanoma over-activates the telomerase gene, so it was expected that longer telomeres would be found in these melanoma cells. However, the study found this mutation produced telomeres that were actually shorter than average.

“This is a surprising finding that opens the door to further enquiry,” said Professor Mann. “It means that there is something else going on; telomerase must control the way telomere length is regulated rather than just make telomeres longer.”

“This finding challenges and adds to our fundamental understanding of telomerase and the role it plays in melanoma and indeed all cancer.”

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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. 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 options are often less effective than for other forms of skin melanoma, so prognosis is often poor.

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.

## **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.