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Melanoma's genetic trajectories are charted in new study

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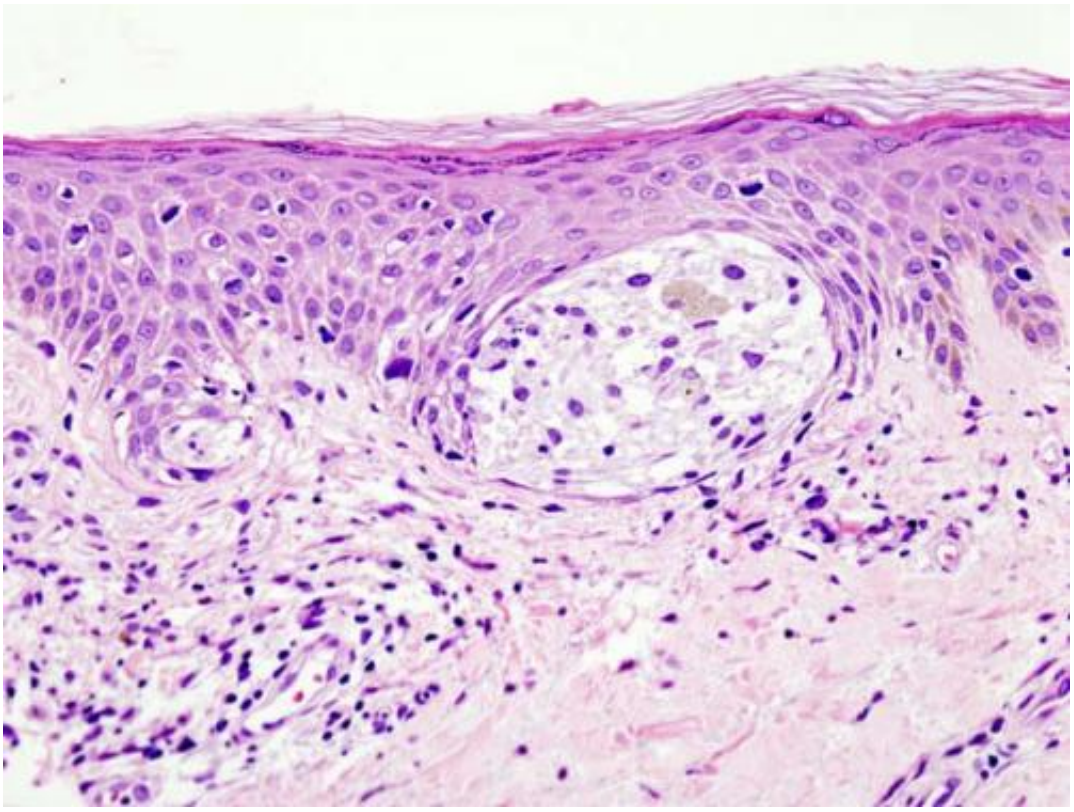

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

An international team of scientists led by UC San Francisco researchers has mapped out the genetic trajectories taken by melanoma as it evolves from early skin lesions, known as precursors, to malignant skin cancer, which can be lethal when it invades other tissues in the body.

By tracing the genetic changes that take place over time in the development of the disease, the research reaffirms the role of sun exposure in the emergence of precursor lesions, such as the common moles known as nevi, but also suggests that continued ultraviolet radiation (UV) damage to benign precursor lesions may push them on a path toward malignancy.

More significantly, the study provides new evidence that genetic and cellular characteristics of skin lesions that are neither clearly benign moles nor malignant melanoma place them in a distinctive intermediate category, the existence of which has been hotly debated among dermatologists and pathologists.

"What happens to patients now is totally unstandardized," said Boris Bastian, MD, PhD, the Gerson and Barbara Bass Bakar Distinguished Professor of Cancer Research at the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC), and senior author of the new study. "Some doctors consider these 'intermediate' types of lesions to be entirely benign, or shave off only part of the lesion and leave some behind. But others treat it as an early melanoma. This work should open the door to understanding how risky these lesions are and when they should be completely removed."

When a melanoma is diagnosed, its precursor lesion is sometimes still present on the skin adjacent to the cancer. As reported in the November 12, 2015 issue of *The New England Journal of Medicine*, the research team took advantage of this unique feature of the disease to identify the genetic differences between precursors and melanoma.

Led by A. Hunter Shain, PhD, a postdoctoral fellow in the Bastian laboratory and HDFCCC member, the scientists gathered skin samples containing both precursor lesions and melanoma that had been obtained from 37 patients, and they then sequenced 293 cancer-causing genes in

150 distinct areas micro-dissected from those samples.

In a clever study design, to determine how genetic analysis would align with standard techniques used in melanoma diagnosis, each of these 150 areas was independently examined through microscopes by eight pathologists specializing in skin disease. The pathologists assigned each area to four main categories ranging from "benign" to "invasive melanoma" based on their judgments of how far the cells in each area had progressed toward malignancy.

Intriguingly, in all of the 13 areas that were unanimously assessed as benign by the pathologists, the researchers found only a single pathogenic mutation, one called BRAF V600E, which has long been associated with melanoma. Based on these data, this single alteration in the BRAF gene appears to be sufficient for the formation of a nevus, the term for a common mole that can sometimes progress to melanoma.

Likewise, there was quite good agreement among the pathologists regarding invasive melanomas, which on genetic analysis were found to contain a large number of point mutations—alterations of a single genetic "letter"—affecting many genes, as well as a significant number of copy-number alterations, in which sizeable segments of the genome containing genes are either deleted or duplicated.

As expected, most disagreement among the pathologists was seen in their assessments of non-invasive melanomas (known as "in situ" melanomas) and so-called intermediate lesions, which were sub-classified as "probably benign" or "probably malignant."

But the genetics of these lesions presented a clearer picture: in most cases, BRAF mutations, most often the V600E mutation seen in the benign lesions, were accompanied by additional pathogenic mutations, but not the full set observed in invasive melanoma. In particular, many

BRAF mutations in the intermediate lesions were accompanied by mutations in a gene known as TERT. The TERT gene helps to set the limits of cell division, and the gene has been implicated in a number of types of cancer.

Moreover, while the researchers found more point mutations in intermediate lesions than in benign moles, there were far fewer point mutations in intermediate lesions than in invasive melanomas, and copy-number alterations were rare.

"There's good agreement between the pathologists' assessments at the extremes of the spectrum, but less so with intermediate lesions," said Shain. "On a genetic level, however, this work clearly shows that there are intermediate lesions. These things really exist—it's not a binary situation."

Mutations caused by UV damage have a distinctive genetic "signature," and in another significant finding, the researchers observed this signature in cancer-causing genes at every stage of melanoma progression.

"A lot of melanomas have been sequenced at this point, and while it's clear they carry UV-induced mutations, no one knew when they occurred," Bastian said. "This study shows that they occur in benign moles, in the melanoma that arises from these moles, and in intermediate lesions. UV both initiates and causes the progression of melanoma, so exposing even benign moles to the sun is dangerous."

According to Shain, the new study's findings on UV-induced mutations provides additional grounding to well-documented aspects of melanoma epidemiology.

"Kids who are in the sunlight more tend to have a greater number of benign moles, and if they continue to stay in the sunlight, those moles are

more likely to progress to melanoma," Shain said. "This study shows that UV-radiation-induced mutations start to accumulate before a benign mole forms, and that UV-radiation-induced mutations continue to drive the progression of some benign and intermediate lesions towards melanoma. So exposing even benign moles to UV is not without risk."

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