Inherited genetic markers may predict melanoma survival—and help plot course of disease

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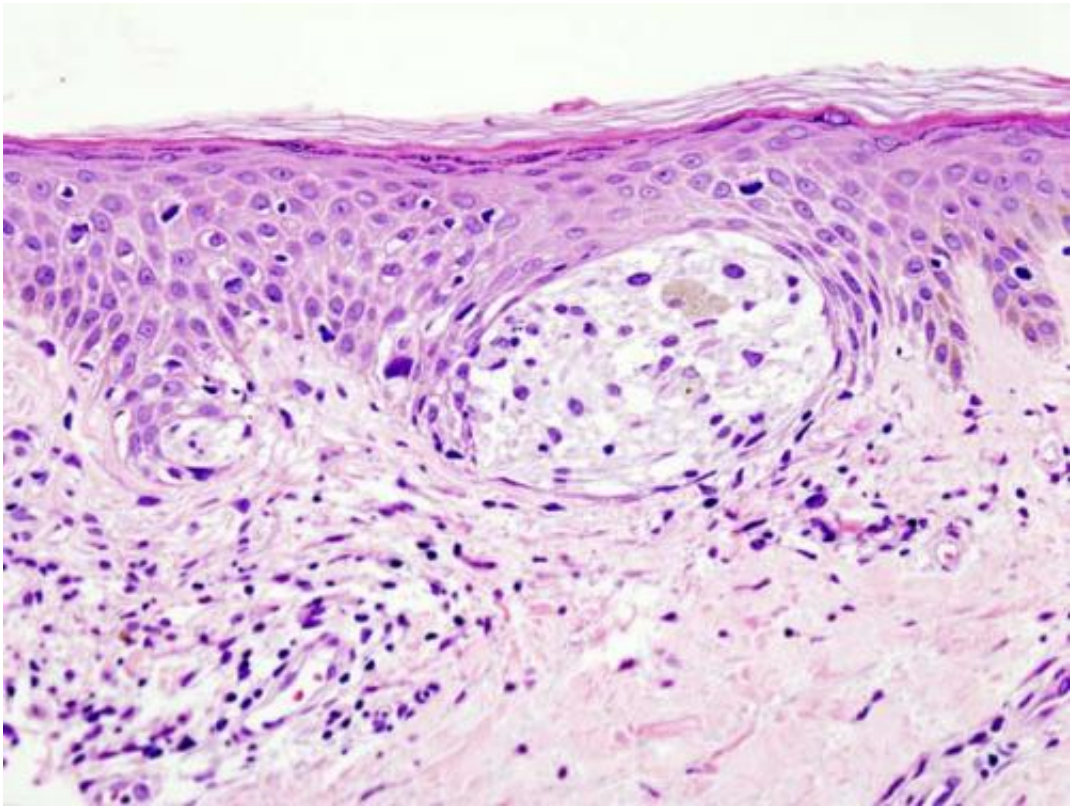

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

Melanoma is the most dangerous and lethal form of skin cancer. But just how long will a patient survive following the removal of a melanoma

tumor?

A more definitive answer to that question could come from new studies at NYU Langone Medical Center and its Laura and Isaac Perlmutter Cancer Center. Researchers there have discovered an inherited genetic marker that might provide clinicians with a personalized tool to gauge an individual's survival and determine which patients require closer monitoring in the years following surgery.

The study, reported online in the journal *Clinical Cancer Research*, is one of the first to provide strong evidence for the use of genetic markers to improve melanoma prognostication, complementing currently available tools used in clinical practice.

"There are gene variants that we inherit from our parents that don't increase our susceptibility to developing melanoma, but once the diseases strikes, they can alter outcome " says senior author Tomas Kirchhoff, PhD, Assistant Professor in the Department of Population Health at NYU Langone and a member of the Perlmutter Cancer Center.

While representing only four percent of all skin cancers, melanoma accounts for 80 percent of skin cancer deaths. And although recent advances in the treatment of melanoma have led to unprecedented improvements in survival, it remains critically important to know which earlier stage patients are at greatest risk. However, at present, risk assessment is limited to a set of clinical and pathological tests that are not specific or sensitive enough to tailor melanoma prognosis to individual patients.

The key to melanoma's progression is its ability to trick the immune system and escape its surveillance. For this reason, the NYU Langone researchers focused on inherited genetic markers found in the pathways of the body's immune response.

"We hypothesized that if someone inherits a certain genetic variant that suppresses immunity, there is a much higher chance that once melanoma strikes, it will progress faster," Kirchhoff says.

Kirchhoff and his colleagues began their search for inherited genetic markers by surveying nearly 400 gene variants, called expression quantitative trait loci (eQTLs), which are involved in immune regulation in humans. These inherited genetic markers are located in areas of the human genome that do not directly produce proteins—the so-called noncoding DNA—but do affect the activation of genes located nearby.

To further narrow their search for gene variants, Kirchhoff and his team took advantage of a database from the MuTHER (Multiple Tissue Human Expression Resource) project, a UK-based initiative that contains eQTL data collected from a large number of normal twins from a healthy population.

The genetic variants that showed the most significant correlation with the activation of nearby immune genes in the normal twin population were tested in samples collected from 1,221 patients at NYU Langone's Interdisciplinary Melanoma Cooperative Group, directed by study co-author Iman Osman, MD, Professor of Dermatology, Medicine, and Urology at NYU Langone.

Two of these gene variants showed significant association with melanoma survival, and the prediction of melanoma survival was strongest when both gene variants were tested together in the human samples. "This joint test showed that the two markers do not fully correlate with established pathological predictors, suggesting their independent clinical relevance," Kirchhoff says.

Kirchhoff and his colleagues identified a specific combination of the two markers, called genotypes, appearing in about 60 percent of the

human population, which was associated with less favorable, shorter survival in the melanoma patients they tested. By contrast, the remaining 40 percent of patients with the alternative genotype had on average five years better survival.

Interestingly, both genetic variants are located in a region on chromosome 1 that contains a tightly packed cluster of five "interleukin" genes, which regulate the immune response. The NYU-Langone researchers found that the less favorable genotypes for the two genetic variants associate with decreased activation of two interleukin genes in this region, IL10 and IL19.

"We strongly suspect that the genetic variants we identified impact balanced activation of these interleukins, which could play a major role in the progression of melanoma towards more aggressive, metastatic disease," Kirchhoff says. "In turn, this imbalanced immunity determines, or modulates, melanoma survival."

The next step in this research will be to replicate these observations in a much larger group of patients. The researchers believe they might, in the near future, be able to target these two markers in treatments at early melanoma stages in patients at high risk of poor outcomes. The novel approach they applied in the melanoma study also can be extended to the discovery of prognostic markers in other types of cancer.

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