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Genomic discovery of skin cancer subtypes provides potential 'signpost' for drug targets

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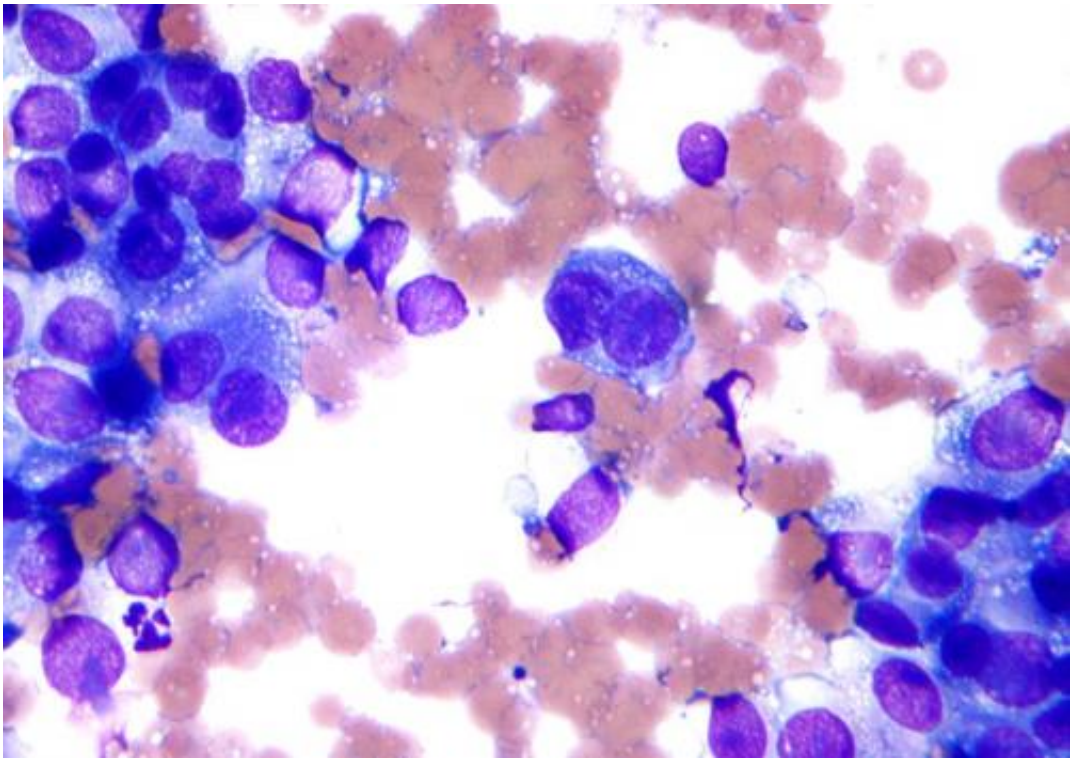

Micrograph of malignant melanoma. Cytology specimen. Field stain. Credit: Nephron/Wikipedia

Cutaneous melanoma, the most deadly form of skin cancer, is now believed to be divided into four distinct genomic subtypes, say researchers at The University of Texas MD Anderson Cancer Center, a finding that could prove valuable in the ever-increasing pursuit of personalized medicine.

As part of The Cancer Genome Atlas, researchers identified four melanoma subtypes: BRAF, RAS, NF1 and Triple-WT, which were defined by presence or absence of mutations from analysis of samples obtained from 331 patients. The five-year study resulted from an international collaboration of over 300 researchers from more than five countries, including Australia, Germany and Canada.

"A major achievement in the clinical management of patients with advanced melanoma has been the development of effective targeted therapies," said Jeffrey E. Gershenwald, M.D., professor of surgery, Surgical Oncology. "This comprehensive classification of melanomas allows us to create a framework that could be used to further personalize therapeutic decision-making in both the targeted and immunotherapy arena, as well as to develop more impactful prognostic and predictive models to inform patient care."

Results from the study are published in the June 18 issue of *Cell*. Analysis of the TCGA effort was chaired by Gershenwald, Ian Watson, Ph.D., instructor of Genomic Medicine and Lynda Chin, M.D., former chair of Genomic Medicine and now associate vice chancellor for health transformation and chief innovation officer for health affairs at The UT System. Gershenwald is also co-leader of MD Anderson's Melanoma Moon Shot Program, which aims to accelerate the conversion of scientific discoveries into clinical advances and significantly reduce cancer deaths.

The scientists found all four genomic subtypes share common 'downstream' signaling pathways, but differ in how they activate these pathways. Understanding the genomic underpinnings of melanoma may provide additional information on other existing therapies.

"For example, BRAF and MEK inhibitor combinations are now used to treat patients with BRAF mutant melanomas, and MEK inhibitor

combinations are being explored for RAS mutant melanomas," said Watson. "Pre-clinical studies have already demonstrated that some NF1 melanoma cell lines respond to MEK inhibitors, but more work is needed to identify responders and non-responders within this new melanoma subtype, as well as to determine strategies to treat Triple Wild-type melanoma patients."

Interestingly, no significant correlation was found between the genomic subtypes and patient outcome. However, within each genomic subtype, they found a subset with evidence of immune infiltration that did correlate with improved survival.

"Detailed analyses showed that these lymphocytic elements were not merely 'bystanders,"' said Chin. "They had infiltrated the tumor and were likely associated with melanoma biology." The study also revealed the importance of a T cell biomarker called LCK, a protein found in lymphocytes or white blood cells. The biomarker was shown to be associated with improved patient survival.

The team hypothesizes that this information could prove useful in the emerging field of immunotherapy, which has shown success in treating late-stage melanoma patients. In particular, recently approved checkpoint blockade drugs have shown incredible potential in treatment for melanomas. Yet, it is not entirely clear which patients respond to the therapy.

"We believe this international collaboration from more than 20 tissue source sites and 50 institutions around the globe, which included pathologists who analyzed samples for immune infiltration, computational biologists who identified significant driving genetic alterations, and clinician scientists who aided in acquiring samples and interpreting data, have generated a dataset that is a treasure trove, and that will seed studies for many years to come," said Chin. "We could not

have carried out this study without the families and patients who donated samples by participating in research protocols."

Provided by University of Texas M. D. Anderson Cancer Center