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New Strategy Developed To Diagnose Melanoma

ScienceDaily (Apr. 3, 2009) — A UCSF research team has developed a technique to distinguish benign moles from malignant melanomas by measuring differences in levels of genetic markers. Standard microscopic examinations of biopsied tissue can be ambiguous and somewhat subjective, the researchers say, and supplementing standard practice with the new technique is expected to help clarify difficult-to-diagnose cases.

In a large study of previously diagnosed cases, the new technique distinguished between benign, mole-like skin lesions and melanomas with a success rate higher than 90 percent. It also succeeded with most of the previously misdiagnosed cases, which were among the most difficult to distinguish.

This is the first large-scale study to demonstrate both the high diagnostic accuracy and practicality of a multi-biomarker approach to melanoma diagnosis, said Mohammed Kashani-Sabet, MD, professor of dermatology at UCSF and director of the Melanoma Center at the UCSF Helen Diller Family Comprehensive Cancer Center.

Kashani-Sabet is lead author on a paper reporting the new finding in the *Proceedings of the National Academy of Sciences*, which is scheduled for online publication the week of March 30, 2009. The paper also will appear in a future print issue of PNAS.

Melanoma is the deadliest form of skin cancer. It can spread to almost any organ of the body and is difficult to treat in its advanced stages. Progress in survival rates has been made principally through earlier diagnosis. The genomics-based approach combined with current diagnostic practice can aid earlier detection and contribute to more accurate assessment, report the UCSF scientists who developed the diagnostic tool.

The molecular diagnosis strategy is now being developed for clinical use by a diagnostics company.

To develop the diagnostic tool, the researchers first used a microarray – a "gene chip" -- to identify about 1,000 human genes that were present at different levels in malignant melanomas compared to benign moles. They narrowed their study down to five genes that all showed higher levels of activity in melanomas than in moles and could be studied with standard antibody techniques.

Focusing on the proteins produced by the five genes, they stained the proteins with antibodies to assess the level of gene expression in mole and melanoma tissues. The new diagnostic technique distinguished moles from melanomas by differences in both the level and the pattern of activity of the five proteins.

To develop and test the diagnostic technique, the researchers examined levels of the five biomarkers in 693 previously diagnosed tissue samples. To ensure that the diagnosis based on tissue examination had been correct, all samples were reviewed by the study's pathologist. They analyzed the samples with the new

procedure and found that the increased protein production by the melanomas compared with the moles was statistically significant, and thus a reliable diagnostic indicator. Unexpectedly, the proteins also showed different patterns of activity in the two types of tissue, yielding a second, even more discriminating diagnostic indicator.

"We hoped for clear diagnostic differences in the intensity of gene expression," Kashani-Sabet said. "We found what we had hoped for, but then we got a bonus. The pattern of protein activity from the top to the bottom of the tissue was strikingly different between the benign and the malignant tissue, providing an additional trait valuable for diagnosis."

Although some of the genes and their proteins were stronger indicators than others, the research team found that the combination of all five achieved the highest diagnostic accuracy. The multi-biomarker diagnostic correctly diagnosed 95 percent of the benign moles -- a measure known as specificity. The accuracy rate was 91 percent for diagnosing malignant melanomas -- the sensitivity rate. In addition, the strategy correctly diagnosed 75 percent of the most difficult cases, which had previously been misdiagnosed. The technique also accurately diagnosed other difficult-to-diagnose moles, known as dysplastic and Spitz nevi.

"We have a test that can help patients and help clinicians who treat melanoma," said Kashani-Sabet. "With this added diagnostic tool we can shed light on lesions that are difficult to classify and diagnose."

Co-authors on the paper and collaborators in the research, all at UCSF, are Javier Rangel, MD, resident in dermatology; Mehdi Nosrati, BS, staff research assistant; and Sima Torabian, MD, a former post-doctoral research fellow in the Kashani-Sabet lab.

Also, Jeff Simko, MD, associate professor of clinical pathology; Chris Haqq, MD, PhD, assistant adjunct professor of urology; James Miller, PhD, statistical consultant; Richard Sagebiel, MD, professor of dermatology and pathology; Dan Moore, PhD, statistical consultant; and David Jablons, MD, professor of surgery.

A patent has been filed by UCSF covering the use of these five genetic markers in melanoma diagnosis. The patent has been licensed to Melanoma Diagnostics, based in Fremont, Calif. Lead author Kashani-Sabet owns stock in this company. Co-author Miller has an ownership interest in MDMS, a software company in Arizona that provided the software to generate diagnostic algorithms.

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