Genetics Sheds Light on Lentiginosis Syndromes

BY JEFF EVANS
Senior Writer

WASHINGTON — Conditions in which patients have multiple lentigines commonly have an etiology that shares the same final molecular pathway that predisposes the patients to tumors, Dr. Constantine Stratakis said at a meeting of the Society for Pediatric Dermatology.

Understanding the common etiologic pathway in lentiginosis syndromes may help in developing therapeutic strategies and identifying individuals with less frequent or nonclassic presentations of such syndromes, said Dr. Stratakis, head of the section on endocrinology and genetics and chief of the heritable disorders branch at the National Institute of Child Health and Human Development, in Bethesda, Md.

Some inherited (and sporadic) lentiginoses such as a labial melanotic macule (J. Am. Acad. Dermatol. 1993;28:33-9) or genital lentiginosis (J. Am. Acad. Dermatol. 1990;22:453-60) are not tied to other lesions or tumors and are frequent in the population. Another condition not linked with tumors is benign lentiginosis, an autosomal dominant condition that is more frequently found in blacks and people of mixed race. Its molecular etiology is unknown. But other lentiginoses have more phenotypic variability and are associated with a predisposition to tumors:

► **Peutz-Jeghers syndrome.** Not all of the patients who have this autosomal dominant condition associated with mutations or deletions of the STK11/LKB1 gene have classic lip pigmentation.

"You really have to look for the distribution of unusual-looking pigmented lesions that may not be obvious," Dr. Stratakis said. "The distribution of the lesions is very important. It's not just the classic pigmented macules that you all know from textbooks." Other classic features of this condition include hamartomatous colonic polyps and a predisposition to a variety of neoplasms.

► **LEOPARD syndrome.** Many individuals who are affected by this condition may have only some of the phenotypic characteristics that have been described (Lentigines, ECG abnormalities, Ocular hypertension, Pulmonary stenosis, Abnormal genitalia, Retarded growth, and Deafness). For example, they may exhibit deafness and ECG abnormalities and no other phenotype.

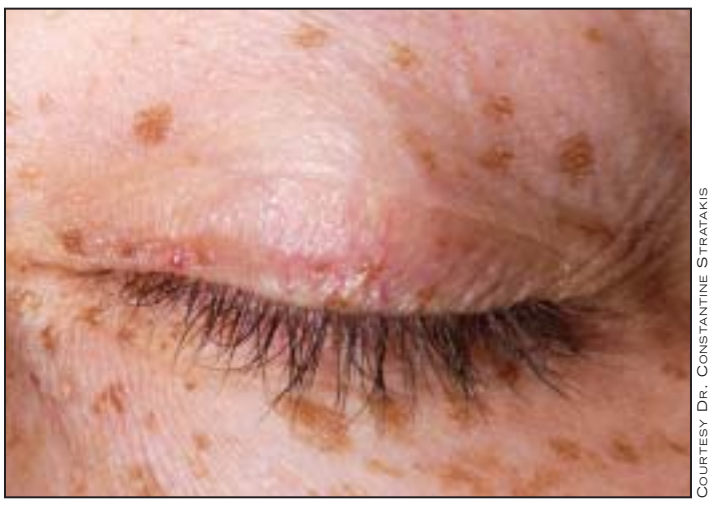
Many patients thought to have LEOPARD syndrome have been recognized to have Watson syndrome, a condition that presents with pulmonary stenosis and inherited lentiginosis but is actually a form of neurofibromatosis type 1 (NF-1). It is now known that almost all the patients identified with pulmonary stenosis, multiple lentigines, and a predisposition to tumors have NF-1 gene mutations or deletions (Am J. Med. Genet. A. 2006;140:2749-56).

But patients with classic LEOPARD syndrome (without NF-1 gene mutations or deletions) have mutations in the same gene that causes Noonan's syndrome: the PTPN11 gene (which codes for a protein tyrosine phosphatase). There is some phenotype-genotype correlation in that mutations in slightly different locations of the PTPN11 gene are responsible for the LEOPARD and Noonan's syndromes.

"That explains why … whenever I was getting patients with Noonan's, I would almost always detect lentigines in these patients, except that very few of them had the density and the intensity of the pigmented lesions that the patients with classic LEOPARD have," he said.

Since not all patients with LEOPARD or Noonan's fill all the diagnostic criteria for these disorders, one must make diagnosis using signs that are not classic for either condition. Patients with LEOPARD frequently have skeletal defects or joint hyperextensibility and other collagen disorder–like defects that can be seen in patients with Marfan syndrome, Ehlers-Danlos syndrome, and similar conditions.

"Almost all LEOPARD patients that I have seen have a form of skeletal dysplasia and/or some degree of flexibility," he said.



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This patient with Carney's complex shows lentigines on the eyelids as well as a small, red myxoma on the upper lid.

► **Cowden disease.** The lentigines that are found in individuals with this disease are "for the most part indistinguishable from the lentigines in these other conditions," Dr. Stratakis said. An autosomal dominant expression of a mutation in the PTEN gene (a protein tyrosine phosphatase) also causes this disease's characteristic multiple hamartomas and predisposition to a variety of tumors. Another condition with a PTEN gene mutation is the Ruvalcaba-Myhre-Smith syndrome, in which patients have penile lentiginosis.

"This gene can be mutated in a variety of phenotypes [called the PTEN mutation hamartoma syndromes] that don't necessarily make any sense," Dr. Stratakis said. "Yet there is one thing that all these phenotypes have in common … and that is lentigines. All of these conditions that have multiple lentigines and have a predisposition to tumors in essence are candidates for PTEN testing," he said.

► **Carney's complex (CC).** Patients with this multiple endocrine neoplasia syndrome have multiple lentigines, which do not necessarily have a distinct presence on the face. In Dr. Stratakis' experience with about 500 CC patients, it has become clear that they do not have the same type of pigmentation seen in Peutz-Jeghers patients, even though some features of the two conditions may be overlapping.

CC patients have "very distinct and purer labial macules, and some have no distinct pigmentation of the face," except for a particular distribution and a few blue nevi on the saddle of the nose, which would be unusual for the general population, according to Dr. Stratakis.

Multiple genital macules are present in CC patients, in contrast to one or two at most in the general population. Ear and outer canthal pigmentation is present in about one-third of CC patients but also occurs infrequently in Peutz-Jeghers patients.

CC patients have mutations in the PRKAR1A gene; PRKAR1A is a regulator of protein kinase A and mutations cause dysregulation of the catalytic subunit of the enzyme. A mouse model confirmed that the mutated gene could cause a variety of tumors. Subsequent experiments showed chromosomal instability and other features caused by PRKAR1A gene mutations in human and mouse cells.

If very different genes that do not seem to have a "functional connection" cause all of these inherited lentinginosis syndromes, "then they must have a common mediator of tumorigenesis," Dr. Stratakis said. "It turns out that the common mediator is mTOR," which is the mammalian target of rapamycin. Indeed, it appears that all of these conditions are associated with dysregulation of mTOR activity, which normally regulates other tumor suppressor genes and oncogenes. Rapamycin and its analogues are being tested in clinical trials of cancer patients, Dr. Stratakis noted. ■

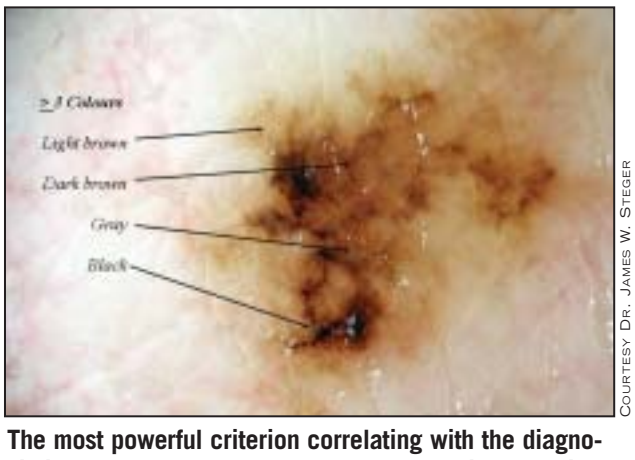
Dermatoscopy Plus a Clinical Exam Detect Melanoma Best

BY DOUG BRUNK
San Diego Bureau

CORONADO, CALIF. — Dermatoscopy can identify melanomas as small as 3 mm, but should be combined with a careful exam for the best diagnosis, Dr. James W. Steger said at an update on melanoma sponsored by the Scripps Clinic.

Researchers evaluated 349 consecutive patients who had 375 suspicious lesions requiring biopsy. Of these, 161 were 6 mm or smaller and 13 were melanomas. Clinical diagnosis alone detected 10 of 13, for a sensitivity of 77% and a specificity of 74%. Dermatoscopy alone also detected 10 of 13. Clinical and dermatoscopy criteria combined detected all 13 (Eur. J. Dermatol. 2002;12:573-6).

In a follow-up study, the researchers compared clinical exam with dermatoscopy for diagnosing 203 sequential pigmented lesions smaller than 3 mm in diameter (Br. J. Dermatol. 2006;155:570-3). In this study, 10 of 23 melanomas were diagnosed by clinical exam alone while dermatoscopy using Menzies score picked up 19 of the 23, which means that, for "very small melanoma [3 mm and under] the diagnostic rate of dermatoscopy is about double what it is for the naked eye," said Dr. Steger, chair of the department of dermatology at Naval Medical Center San Diego. He then discussed two easy screening algorithms in dermatoscopy.



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The most powerful criterion correlating with the diagnosis is the presence of three or more colors in the lesion.

The first is the three-color test. After review of 74 pigmented lesions referred for excision, the most powerful criterion correlating with a histopathologic diagnosis of melanoma was the presence of three or more colors seen in the lesion on dermatoscopy. Sensitivity was 92%. Specificity was only 51% (Br. J. Dermatol. 2002;146:481-4).

"That's okay, since this is a screening technique," Dr. Steger said.

The second algorithm is the three-criteria checklist. Criteria include asymmetry of color or dermoscopic structures, atypical pigment network, a "tennis net–like" pattern of irregular holes and thick lines, and the presence of any type of blue or white colors (Dermatology 2004;208:27-31).

Six nonexperts underwent 1 hour of training and applied the criteria to 231 consecutively excised pigmented lesions. Results were compared with those of an expert who used dermatoscopy with the pattern analysis method of diagnosis.

The nonexperts had a sensitivity of 96% and a specificity of 33%. The expert had a sensitivity of 90% and specificity of 94% using dermatoscopy. ■