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. Constantinos 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) lentigines, such as a labial melanotic macule (J. Am. Acad. Dermatol. 1993;28:33-9) or lentiginosis, are associated with tumors and are frequent in the general population, according to Dr. Stratakis.

But other lentigines have more phenotypic variability and are associated with predispositions to tumors.

■ Peutz-Jeghers. 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 hamartomaticous colonic polyps and a predisposition to a variety of neoplasms.

■ LEOPARD syndrome. Many individuals with a predisposition to tumors may have only some of the phenotypic characteristics that have been described (Lentigines, ECG abnormalities, Ocular hypertelorism, 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 Wason syndrome, a condition that presents with pulmonary stenosis and inherited lentigines 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 phenotyp-genotype correlation in that mutations in slightly different locations of the PTPN11 gene are responsible for the LEOPARD and Noonan 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 pulmonary stenosis 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 hyperflexibility and other collagen disorder-like defects that can be seen in patients with Marfan syndrome, Ehlers-Danlos syndrome, and similar conditions.

“All almost LEOPARD patients that I have seen have a form of skeletal dysplasia and/or some degree of flexibility,” he said.

Dermatoscopy Plus a Clinical Exam Detect Melanoma Best

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. 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 melanomas [3 mm and under], the diagnostic rate of dermatoscopy is about double that of the diagnosis,” said Dr. Steger, chair of the department of dermatology at Naval Medical Center San Diego. He then discussed two easy screening algorithms in dermatoscopy.

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 excited pigmented lesions. Results were compared with those of an expert who used dermatoscopy with the pattern analysis method.

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