Genetics Sheds Light on Lentiginosis Syndromes

BY JEFF EVANS
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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) lentiginoses present in a labial melanotic macule (J. Am. Acad. Dermatol. 1993;28:33-9) or lentigo simplex to a variety of neoplasms. Results were compared with those of an expert dermatoscopy. Sensitivity was 92%.

The nonexperts had a sensitivity of 96% and a specificity of 94% using dermatoscopy. 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 pigmentations 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 genitai 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 PTEN gene mutations or mutations in the PTEN gene (which codes for 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 VulvaCabaMyhren-Smith syndrome, in which patients have penile lentigines.

“Just as 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 the 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 hypertelorism, Pulmonary stenosis, Abnormal genitalia, Retarded growth, and Deafness). For example, they may exhibit deafness and ECG abnormalities and not other phenotype.

Many patients thought to have LEOPARD syndrome have been recognized to have Noonan’s syndrome, a condition that presents with pulmonary stenosis and inherited lentigosis 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.

“Almost all LEOPARD patients that 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 hyperextensibility and other collagen disorders—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.

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%.

Sensitivity 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 dermatoscopic structures, atypical pigmented 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.

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.

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 VulpavakaMyhren-Smith syndrome, in which patients have penile lentigines.

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