Expert Reviews Diagnosis of Genodermatoses

BY KERRI WACHTER

Genodermatoses may be rare, but it is still important to be familiar with the signs typically seen in patients, according to Dr. Kara N. Shah. “You will see these patients in your practice. The important thing is recognizing them,” said Dr. Shah, a pediatric dermatologist at the Children’s Hospital of Philadelphia. She shared the following characteristics and information about causative genes for genodermatoses:

**Goltz Syndrome**

The characteristic features of Goltz syndrome, or focal dermal hypoplasia, include areas of focal atrophy with fat herniation, unusual pigmentation and inflammatory dermatoses, raspberry-like papillomas, scalp anomalies, a range of dental and ocular abnormalities, sparse hair, short stature, and mental retardation in some patients. The condition is known to be X-linked dominant and lethal in most males.

The genetic defect responsible for this condition has been identified as a mutation in the PORCN gene, which is a member of the porcine gene family that encodes transmembrane endoplasmic reticulum proteins that target Wnt signaling proteins. Wnt proteins are key regulators of embryonic development.

“There are patients who have been shown to have somatic or postzygotic mosaicism. … Only a subset of cells are affected and they tend to have a milder phenotype,” Dr. Shah said.

**Hyper-IgE Syndrome**

Hyper-IgE syndrome is characterized by chronic eczematous dermatitis, recurrent abscesses due to Staphylococcus aureus, and recurrent sinus and lung infections (with pneumatoceles). Dental abnormalities, fractures, and scoliosis are also common. Mutations in the signal transducer and activator of transcription 3 gene (STAT3) have been associated with this disorder. STAT3 is important in the JAK-STAT cytokine signaling pathway, according to Dr. Shah.

Patients who are deficient in STAT3 have deficient activation of several cytokines and reduced production of beta-defensins, leading to susceptibility to S. aureus and Candida skin infections.

**NF-1-Like Syndrome**

Neurofibromatosis type 1-like (NF-1-like) syndrome shares the neurofibromatosis type-1 characteristics of multiple café-au-lait spots, axillary freckling, and macrocra. Additional features include a Noonan-like dysmorphic psychomotor developmental and learning difficulties. These patients, however, do not seem to develop some other NF-1 characteristics, such as Lisch nodules in the iris, neurofibromas, and central nervous system tumors.

NF-1-like syndrome is an autosomal dominant condition. Patients with NF-1-like syndrome carry mutations in the SPRED-1 gene, including nonsense frameshift, splicing mutations, and in-frame deletions. The SPRED-1 protein negatively regulates Ras-mitogen-activated protein kinase (MAPK) signaling, similar to neurofibromin, the defective protein in patients with NF-1, Dr. Shah said.

**Ras-MAPK Syndromes**

Ras-MAPK syndromes (neuro-cardio-facial-cutaneous syndromes) include NF-1 and NF-1-like syndromes, Noonan syndrome, LEOPARD syndrome, and others. Ras is activated by cell surface receptors; activation of Ras signaling causes cell growth and differentiation, and it affects cell survival, Dr. Shah said. The name LEOPARD highlights the main features of the disorder: lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, and deafness. “The important thing to recognize early on is the similarities with regard to some of the dysmorphic facial features … developmental issues, cardiac anomalies, or skeletal anomalies,” she said.

Molecular studies have shown that LEOPARD is an allelic disorder caused by mutations in PTPN11 and RAF1.

The key features of Noonan syndrome include unusual facial features (ocular hypertelorism, down-slanting eyes, webbed neck), congenital heart disease (in 50%), short stature, and chest deformity. Mental retardation also may occur, according to Dr. Shah. Skeletal, neurologic, genitourinary, lymphatic, eye, and skin findings may be present to varying degrees. Although the pathophysiology of Noonan syndrome is not fully understood, four disease-causing genes (PTPN11, SOS1, RAF1, and KRAS) have been identified. These genes are part of the RAS transduction pathway.