LEOPARD syndrome

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Identity

Alias
Multiple-lentigines syndrome.
Generalized lentiginosis.
Cardiocutaneous syndrome.
Progressive cardiomyopathic lentiginosis.

Note
LEOPARD syndrome is characterized by multiple lentigines, cardiac anomalies, facial dysmorphisms, abnormalities of the genitalia in males, retardation of growth, and deafness. LEOPARD syndrome shares many features with Noonan syndrome, in which lentigines and deafness usually are not present. Molecular studies have demonstrated that LEOPARD and Noonan syndromes are allelic conditions.

Inheritance
LEOPARD syndrome is an autosomal dominant multiple congenital anomaly syndrome, with high penetrance and markedly variable expression.

Clinics

Phenotype and clinics
The main clinical features of LEOPARD syndrome are multiple lentigines, congenital heart defect or electrocardiographic abnormalities, deafness, facial anomalies, urogenital malformations, skeletal anomalies, retardation of growth, and learning difficulties.
Diffuse lentiginosis is a characteristic of LEOPARD syndrome. Lentigines are brown macules, usually 2 to 8 mm in diameter, generally most heavily concentrated on the upper part of the trunk and neck, although they can also be present on the face, limbs, palms, soles and genitalia. The mucosae are characteristically spared. Lentigines are rarely present at birth and, classically, develop during childhood, increasing in number until puberty and darkening with age. Cafe-au-lait patches as well as axillary freckling have also been described. Structural cardiac defects can be detected in 70% of the patients. Hypertrophic cardiomyopathy is the most common defect. It is progressive and commonly involves the intraventricular septum. Pulmonary valve stenosis with valve leaflet dysplasia, partial atrioventricular canal and mitral valve anomalies can also be present. Arrhythmias include heart block, bundle branch block, and hemiblock.
Deafness is generally sensorineural, may be unilateral, but can be profound. Most cases have deafness diagnosed in childhood, but some are reported to have developed it in adult life.
Facial anomalies include hypertelorism, palpebral ptosis, and large low-set ears. They occur in 90% of the patients.
A high prevalence of genitourinary abnormalities has been reported especially in male patients. These include cryptorchidism, hypospadias, as well as malformations of the kidneys and collecting systems. Pectus carinatum or excavatum are detectable. In old age, there is a tendency to develop thoracic kyphosis. Growth retardation is frequent. The adult height is generally below the 25th centile. Mild mental retardation and learning difficulties, so as language defects related to deafness, can occur in patients with LEOPARD syndrome.
**Legend:** Typical multiple lentigines in a patient with LEOPARD syndrome.

**Neoplastic risk**
A distinct class of somatic mutations of PTPN11, appearing to have high gain-of-function levels, contributes to leukemogenesis. The identification of these mutations at a germlinal level explains the higher prevalence of myeloproliferative disorders and acute leukemia among children with Noonan or LEOPARD syndrome. The RAS/MAPK pathway is deregulated in juvenile myelomonocytic leukemia due to mutations in NRAS, KRAS2 or NF1. It has been hypothesized that germline or somatic mutations in PTPN11 could also interfere with RAS/MAPK pathway.

Multiple granular cell myoblastomas, a tumor believed to arise from Schwann cells, have been reported in one patient.

Central giant cell granulomas presenting as cyst-like lesions in the mandible have also been described in LEOPARD syndrome.

Choristoma, a congenital corneal tumor containing cellular elements of ectodermal derivatives, may occasionally coexist with LEOPARD syndrome.

**Treatment**
Beta-blockade or calcium channel blockers are most frequently used in treatment of obstructive cardiomyopathy. If there is no response to drug therapy, surgery for left ventricular outflow obstruction or transplantation can be indicated.

The use of lasers has been shown to be effective in the treatment of lentigines. Noninvasive agents such as tretinoin cream and hydroquinone cream used in combination have been shown to lighten lentigines after several months of application.

**Prognosis**
The prognosis is mainly determined by the nature and severity of cardiac lesions. In fact, the major concern is that of hypertrophic cardiomyopathy, because of its association with arrhythmia and sudden death.

**Cytogenetics**

**Note**
Chromosome analysis is normal in patients with LEOPARD syndrome.

**Genes involved and proteins**

**PTPN11**

**Alias**
Protein-tyrosine phosphatase, nonreceptor-type, 11

**Location**
12q24.1

**DNA/RNA**
Description: It contains two Srd homology 2 (SH2) domains and a protein tyrosine phosphatase domain (PTP); 15 exons.

**Protein**
Description: 593 amino acids, 68 kD.

Expression: Highly expressed in human tissues, particularly abundant in heart, brain, and skeletal muscle.

Function: The protein-tyrosine phosphatases are a highly polymorphic set of molecules having a role in regulating the responses of eukaryotic cells to
extracellular signals. They achieve this by regulating the phosphotyrosine content of specific intracellular proteins. The pathogenetic mechanism that causes PTPN11 mutations to specifically exhibit a dermatological phenotype and preferentially cardiac expression in hypertrophic cardiomyopathy is at present unclear.

Mutations

Germinal: LEOPARD syndrome has proved to be allelic to Noonan syndrome, with two recurrent PTPN11 mutations in exons 7 (Tyr279Cys) and 12 (Thr468Met). Additional mutations in exons 7, 12, and 13, different from the two common mutation hot spots, have been reported as a rare occurrence in the syndrome. All the mutations occur in exons that code for the protein tyrosine phosphatase (PTP) domain. Molecular and biochemical studies have shown that the mutations destabilize the catalytically inactive conformation of the protein, resulting in a gain of function. PTPN11 mutations are detectable in about 90% of patients with LEOPARD syndrome.

References


This article should be referenced as such: