A Novel Missense Mutation in the CYLD Gene in a Spanish Family With Multiple Familial Trichoepithelioma

Brocke-Spiegler syndrome (BSS) includes the combination of spiradenomas, cylindromas, and trichoepitheliomas. It has been postulated that BSS results from defects in the regulation of putative stem cells of the folliculosebaceous-apocrine unit. This follicular dysregulation may give rise to 3 different genodermatoses: familial cylindromatosis (FC), multiple familial trichoepithelioma (MFT), or the classic triad of BSS.

The gene for FC was mapped to chromosome 16q12-q13. At present, 32 different germline mutations in the CYLD gene have been described, 20 in families with FC, 8 in families with MFT, and 4 in families with BSS. Taken together, these observations suggest that these inherited syndromes associated with skin appendage tumors not only share a common genetic basis but also may represent phenotypic variation of the same disease.

Report of a Case. An 8-year-old girl came to our department with her parents. Her mother, grandmother, and 2 aunts were diagnosed as having trichoepithelioma since childhood (Figure 1). The parents of our patient wanted to know if their daughter might harbor any genetic susceptibility for these cutaneous lesions. Blood samples were obtained from available family members and 110 unrelated controls. Genomic DNA was extracted; all coding exons were amplified by polymerase chain reaction; and further sequencing analysis was performed. We identified 1 mutation not previously reported. The mutation was found in all patients but not in the healthy members of this family. The change was a point mutation in exon 20 (G2687C) that resulted in substitution of glycine at 896 by alanine (Figure 2). The mutation was not detected in 110 unrelated controls.

Comment. Herein, we report a novel CYLD gene mutation at nucleotide 2687 that carries out 1 amino acid change at glycine 896 in the 4 affected members of this family but not in the proband. The fact that we have not detected this change in 110 unaffected controls makes a contribution to the genotype-phenotype correlation in MFT.

The CYLD gene is considered a negative regulator of nuclear factor kappa B (NF-κB). Thereby, inhibition or
inactivation of CYLD enhances the action of NF-kB and leads to increased resistance to apoptosis and carcinogenesis.6

To our knowledge, this mutation has not been previously described. The known mutations of the CYLD gene are mostly located in the C-terminal portion.

Germline mutations display tissue-specific function loss. Another possibility would be that the germline mutation determines the tissues where the preferred second hit occurs. When the second hit occurs in eccrine-apocrine cells, the patients become susceptible to multiple cylindromas; in hair follicle cells, the patients exhibit susceptibility to multiple cylindromas or MFT.6

Our study shows the importance of mutation screening of the CYLD gene in patients affected with FC and MFT as well as their relatives to identify early clinical manifestations. Analysis of control volunteers in this report confirms the role of this missense mutation as the cause of this syndrome. Further studies evaluating the effect of this mutation in animal models must be considered.

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A Novel PTPN11 Gene Mutation in a Patient With LEOPARD Syndrome

In 1969, Gorlin et al1 described an autosomal dominant syndrome encompassing multiple lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness, currently known as LEOPARD syndrome (LS). Recently, it has been reported that most cases of LS are probably related to heterozygous mutations of PTPN11 (protein-tyrosine phosphatase, nonreceptor type 11), a gene encoding a tyrosine-phosphatase protein named SHP-2, with 2 particular “hot spots” in exons 7 and 12.2,3 Despite overlapping clinical manifestations, LS is distinct from Noonan syndrome, another PTPN11 gene mutation–related disorder but with a different mutation spectrum. Herein we report the first case to our knowledge of typical LS featuring a new PTPN11 gene mutation.

Report of a Case. A 39-year-old woman with a medical history of deafness and a familial background of Down syndrome in a sister was referred for evaluation of pigmen
tary changes that first appeared during infancy associated with mild facial dysmorphism. Clinical examination disclosed multiple light or dark brown macules of varied sizes scattered throughout her whole body surface including her face, palmoplantar areas, lips, and conjunctiva (Figure 1). There were no lentigines on the other mucous membranes. Facial examination revealed hypertelorism. Electrocardiography showed a first-degree atrioventricular block, whereas heart ultrasound evaluation did not find any valve abnormality. Hearing investigations confirmed sensorineural deafness. There were no urogenital abnormalities, endocrinopathy, or growth retardation. A diagnosis of LS was established based on the presence of 4 criteria.

After obtaining the patient’s consent, we undertook direct sequencing of the PTPN11 coding region and discovered a previously undescribed (to our knowledge) heterozygous missense mutation in exon 13, namely a G1493T transversion leading to an R498L change in amino acid sequence (Figure 2). No genetic analysis of her relatives could be carried out to establish a diagnosis of de novo or inherited mutation.

Comment. The SHP-2 phosphatase plays several important roles in cellular physiologic function, mainly in cell proliferation, differentiation, migration, and adhesion.4-8 This protein contains 2 main domains: a C-terminal protein-tyrosine phosphatase (PTP) domain involved in catalytic activity and 2 N-terminal Src homology 2 (SH2) domains interacting with the PTP domain, keeping it folded and inactive (Figure 2).3 To our knowledge, only 7 PTPN11 mutations have been reported in patients with LS, all of them in the PTP domain in exons 7 (Y279C and Y279S), 12 (T468M and A461T), and 13 (Y290N, Y290C, and Y290S) and 14 (R498Q).

Figure 1. Numerous lentiginous elements scattered throughout the trunk.