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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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 pigmentary 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.6-8 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

A Novel PTPN11 Gene Mutation in a Patient With LEOPARD Syndrome

I
n 1969, Gorlin et al1 described an autosomal dominant syndrome encompassing multiple lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitilia, 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.
(Q506P, Q510E, and Q510G).2,4,10-11 Two of them (Y279C and T468M) represent more than 90% of the identified changes. The mutational site in our patient is close to the PTP-SH2 domains interacting tract and to the previously reported mutations affecting exon 13. Accordingly, this change is probably relevant as to LS pathomechanisms. PTPN11 mutations in Noonan syndrome are likely to result in a gain of function with “permanent” catalytic activity of the protein, whereas recent results unexpectedly suggest that LS-related PTPN11 mutations result in a decrease in the phosphatase function of SHP-2.12-14 Understanding why topographically closely related mutations on the same gene may have opposite functional consequences but still result in close phenotypes will be a rewarding challenge.

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