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

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Brooke-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.[1] 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.[2] At present, 32 different germline mutations in the CYLD gene have been described,[3] 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.[4]

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).[5] Thereby, inhibition or inactivation of CYLD enhances the action of NF-κb 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 eccrineapocrine 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.

REFERENCES

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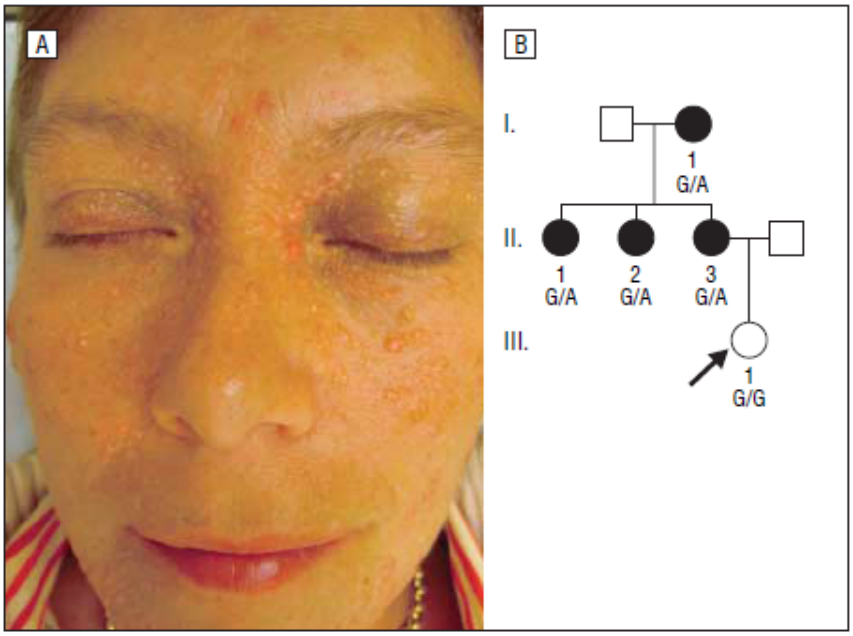

Figure 1. Clinical picture (A) and family pedigree (B) for the present case. A, Multiple trichoepitheliomas are present on the upper eyelids, nose, nasolabial folds, and the upper lip in the mother of the proband. B, Pedigree of the family: for individuals whose DNA samples have been analyzed, the allele sequences at codon 896 have been indicated as G (glycine) or A (alanine). The proband (arrow) encodes for a G on both alleles (G/G), whereas the affected family members are heterozygous for the mutation (black circles) encode an A on the mutant allele.

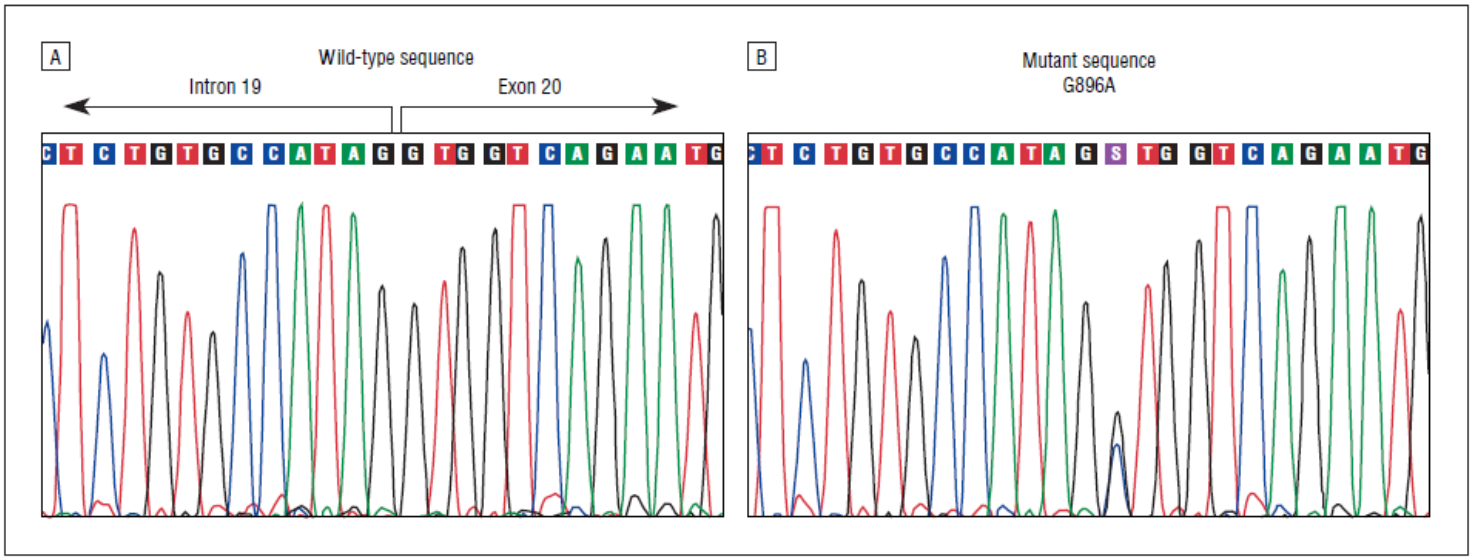

Figure 2. Genetic analysis of the family with multiple familial trichoepithelioma. Shown are wild-type DNA (A) and mutant sequences (B) of exon 20 of CYLD from control and affected members, respectively.