Letters to the Editor

Am. J. Hum. Genet. 64:308, 1999

Variant Manifestation of Cowden Disease in Japan: Hamartomatous Polyposis of the Digestive Tract with Mutation of the *PTEN* Gene

To the Editor:

Because of the clinical heterogeneity and complexity of the group of disorders collectively known as inherited hamartoma syndromes, several attempts have been made to classify them into distinct categories. In the May issue of this *Journal,* Eng and Ji (1998) reviewed recent progress in molecular characterization of these syndromes and classified them into four clinical entities: Cowden disease (CD [MIM 158350]), Bannayan-Ruvalcaba-Riley syndrome (BRR [MIM 153480]), Peutz-Jeghers syndrome (PJS [MIM 175200]), and juvenile polyposis syndrome (JPS [MIM 174900]). Despite some progress in molecular characterization, specific diagnoses of these disorders remain difficult because their phenotypic spectra overlap and because the penetrance of symptoms is age related. Clinical syndromic diagnosis is also dependent on many factors, such as the nature and type of the first clinical symptoms and the medical discipline of the individual(s) diagnosing the syndrome.

PTEN, a gene mapping to 10q23, encodes a dual-specificity phosphatase and is also called *MMAC1* or *TEP1* (Li and Sun 1997; Li et al. 1997; Steck et al. 1997). *PTEN* has been identified as the susceptibility gene for CD and BRR (Liaw et al. 1997; Marsh et al. 1997), and it appears that *PTEN* mutations are detected more frequently in CD and BRR patients when strict clinical criteria are applied to the selection of test subjects (Liaw et al. 1997; Marsh et al. 1997, 1998). *LKB1/STK11,* a serine threonine kinase gene at 19p13.3, has been identified as a susceptibility gene for PJS (Hemminki et al. 1998; Jenne et al. 1998). As for JPS, however, some controversy exists about its molecular basis. Three possibilities have been raised: (1) germ-line mutations of the *SMAD4/DPC4* gene at 18q21.1 are known to be responsible for JPS in some affected families (Howe et al. 1998), (2) *PTEN* mutations appear to be the predisposing elements for some patients diagnosed with JPS (Lynch et al. 1997; Olschwang et al. 1998); and (3) yet another putative locus ("JP1"), centromeric to *PTEN* on chromosome 10q, has been linked to JPS in some affected families (Jacoby et al. 1997). The low penetrance of CD, the sharing of some phenotypic features between CD and JPS, and the possible genetic heterogeneity of JPS make diagnosis complex and confusing.

Pathognomonic hallmarks of CD patients are facial trichilemmomas, acral keratoses, and verucoid or papillomatous papules. This triad of skin lesions occurs in 99% of CD patients (Hanssen and Fryns 1995; Longy and Lacombe 1996). Other, less frequent manifestations of CD include thyroid adenomas or goiters (occurring in 40%–60% of CD patients), breast fibroadenomas (70% of affected females), hamartomatous gastrointestinal polyps (35%–40%), and macrocephaly (38%) (Eng 1998; Marsh et al. 1998). JPS is characterized by gastrointestinal hamartomatous polyps and an increased risk of gastrointestinal cancer (Olschwang et al. 1998).

We examined a 35-year-old Japanese man who had been followed clinically for JPS because of numerous hamartomatous polypoid lesions throughout the entire digestive tract, from esophagus to rectum. Although he had none of the pathognomonic skin lesions of CD, we extended our clinical examination to the patient's whole body and tested him for mutation of the *PTEN* gene, in view of Eng's proposal (1998) that *PTEN* mutation can be a useful diagnostic marker for incompletely expressed CD. After informed consent was obtained, genomic DNAs prepared from blood from the patient and from members of his family were examined by direct sequencing of the entire coding region and exon-intron boundaries of *PTEN,* according to procedures we have described elsewhere (Kurose et al. 1998). The patient's father died of brainstem infarction, a condition unrelated to CD. No other members of his family have been diagnosed as having CD.

The patient was found to be heterozygous for a G→A transition at the second nucleotide of codon 130, which would result in a substitution of Gln for Arg (R130Q). The patient's mother and sister did not carry this mutation (fig. 1), nor was it detected in 192 chromosomes from control Japanese individuals. On closer examination, which included ultrasonography and computed to-

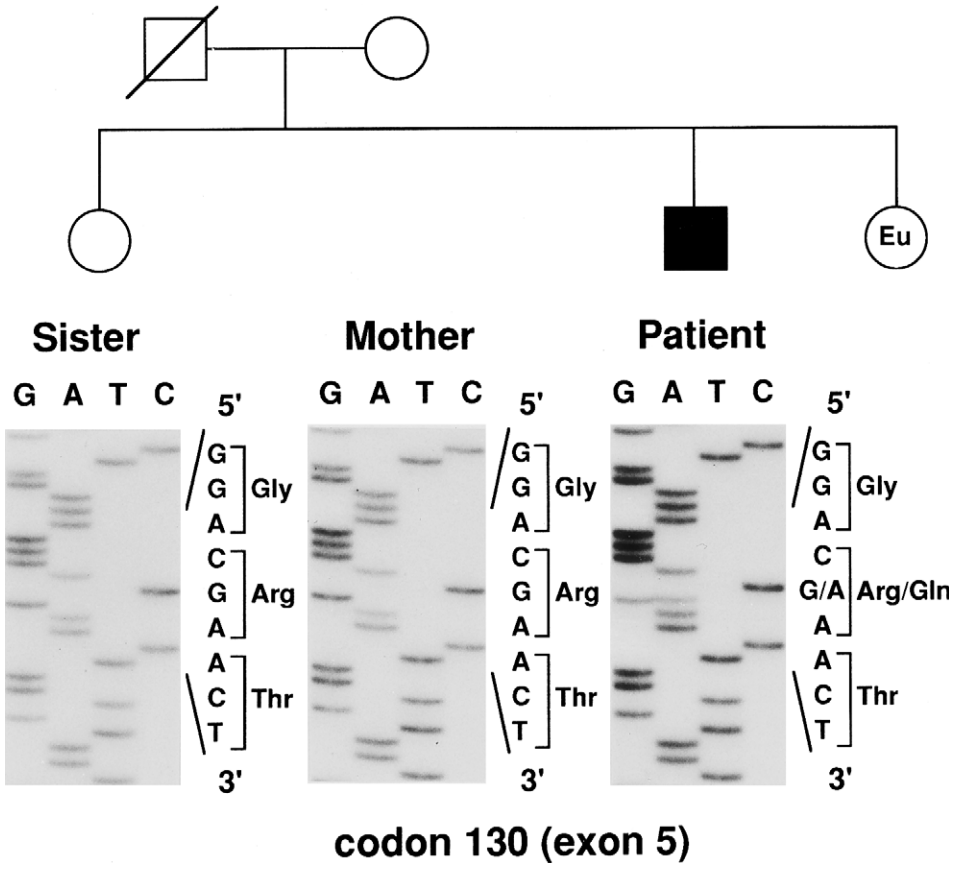

Figure 1 DNA sequencing of the *PTEN* gene in the family of a patient with variant CD. The patient (*blackened square*) carries a G→A transition in exon 5, which is not present in his unaffected mother and sister. Eu: uninformative evaluation.

mography, we found a small thyroid adenoma, a few papillomatous papules in his right hand, and a lung tumor, which is now being examined for possible malignancy. Thus, molecular testing of the *PTEN* gene, as proposed by Eng (1998) in another case of suspected JPS, led us to a diagnosis of CD in a "JPS" patient who manifested atypical symptoms of CD. His germ-line mutation had occurred in the core motif of the phosphatase, at amino acid residue 122–132, encoded by exon 5. Most of the reported germ-line missense mutations of the *PTEN* gene reported in patients with CD have occurred within this core motif (Marsh et al. 1998). Thus, in terms of *PTEN* mutation, our case is typical of a CD entity, although the phenotype is atypical.

Eng and Ji (1998) pointed out that apparent "JPS" patients who carry *PTEN* germ-line mutations (Lynch et al. 1997; Olschwang et al. 1998) may in fact belong to a category of CD patients whose phenotypic features are only partially expressed. Eng and Ji (1998) proposed that the presence of a germ-line *PTEN* mutation could be a good diagnostic sign for CD and BRR. In the future, these inherited hamartoma syndromes should be classified by types of gene mutations, such as the *PTEN* mutation syndrome.

The results described here signal the possibility that a large number of hidden clinical variants of CD may exist among patients who might have escaped correct clinical diagnosis and may have been treated for JPS. Our work underscores the usefulness and importance of molecular methods for achieving differential diagnoses among patients with gastrointestinal polyposis, because JPS and CD predispose to completely different types of cancer.

Acknowledgments

The authors thank the patient and members of his family, for their participation in this study, and Prof. Tetsuro Miki for advice and encouragement. This work was supported by a Grant-in-Aid for priority areas "Cancer Research" and "Genome Science" from the Ministry of Education, Science, Sports and Culture of Japan and by a Research Grant for Cancer Research from the Ministry of Health and Welfare of Japan.

KEISUKE KUROSE,[1,2] TSUTOMU ARAKI,[2] TSUYOSHI MATSUNAKA,[3] YASUHARU TAKADA,[3] AND MITSURU EMI[1]

[1]*Department of Molecular Biology, Institute of Gerontology, and* [2]*Department of Obstetrics and Gynecology, Nippon Medical School, Kawasaki-Tokyo;* [3]*Department of Internal Medicine, Saijo Central Hospital, Saijo, Ehime, Japan*

Electronic-Database Information

Accession numbers and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for CD [MIM 158350], BRR [MIM 153480], PJS [MIM 175200], and JPS [MIM 174900])

References

Eng C (1998) Genetics of Cowden syndrome: through the looking glass of oncology. Int J Oncol 12:701–710

Eng C, Ji H (1998) Molecular classification of the inherited hamartoma polyposis syndromes: clearing the muddied waters. Am J Hum Genet 62:1020–1022

Hanssen AM, Fryns JP (1995) Cowden syndrome. J Med Genet 32:117–119

Hemminki A, Markie D, Tomlinson I, Avizienyte E, Roth S, Loukola A, Bignell G, et al (1998) A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. Nature 391: 184–187

Howe JR, Roth S, Ringold JC, Summers RW, Järvinen HJ, Sistonen P, Tomlinson IP, et al (1998) Mutations in the SMAD4/DPC4 gene in juvenile polyposis. Science 280: 1086–1088

Jacoby RF, Schlack S, Cole CE, Skarbek M, Harris C, Meisner LF (1997) A juvenile polyposis tumor suppressor locus at 10q22 is deleted from nonepithelial cells in the lamina propria. Gastroenterology 112:1398–1403

Jenne DE, Reimann H, Nezu J, Friedel W, Loff S, Jeschke R, Muller O, et al (1998) Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. Nat Genet 18: 38–43

Kurose K, Bando K, Fukino K, Sugisaki Y, Araki T, Emi M (1998) Somatic mutations of the PTEN/MMAC1 gene in fifteen Japanese endometrial cancers: evidence for inactivation of both alleles. Jpn J Cancer Res 89:842–848

Li DM, Sun H (1997) TEP1, encoded by a candidate tumor suppressor locus, is a novel protein tyrosine phosphatase regulated by transforming growth factor β. Cancer Res 57: 2124–2129

Li J, Yen C, Liaw D, Podsypanina K, Bose S, Wang SI, Puc J, et al (1997) *PTEN,* a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science 275:1943–1947

Liaw D, Marsh DJ, Li J, Dahia PL, Wang SI, Zheng Z, Bose S, et al (1997) Germline mutations of the *PTEN* gene in Cowden disease, an inherited breast and thyroid cancer syndrome. Nat Genet 16:64–67

Longy M, Lacombe D (1996) Cowden disease. Report of a family and review. Ann Genet 39:35–42

Lynch ED, Ostermeyer EA, Lee MK, Arena JF, Ji H, Dann J, Swisshelm K, et al (1997) Inherited mutations in PTEN that are associated with breast cancer, Cowden disease, and juvenile polyposis. Am J Hum Genet 61:1254–1260

Marsh DJ, Coulon V, Lunetta KL, Rocca-Serra P, Dahia PL, Zheng Z, Liaw D, et al (1998) Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation. Hum Mol Genet 7:507–515

Marsh DJ, Dahia PL, Zheng Z, Liaw D, Parsons R, Gorlin RJ, Eng C (1997) Germline mutations in *PTEN* are present in Bannayan-Zonana syndrome. Nat Genet 16:333–334

Olschwang S, Serova-Sinilnikova OM, Lenoir GM, Thomas G (1998) PTEN germ-line mutations in juvenile polyposis coli. Nat Genet 18:12–14

Steck PA, Pershouse MA, Jasser SA, Yung WK, Lin H, Ligon AH, Langford LA, et al (1997) Identification of a candidate tumor suppressor gene, *MMAC1,* at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nat Genet 15: 356–362

Address for correspondence and reprints: Dr. Mitsuru Emi, Department of Molecular Biology, Institute of Gerontology, Nippon Medical School, 1-396, Kosugi-cho, Nakahara-ku, Kawasaki, 211-8533, Japan. E-mail: memi@nms.ac.jp

0002-9297/99/6401-0041$02.00