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INVITED EDITORIAL
Molecular Classification of the Inherited Hamartoma Polyposis Syndromes: Clearing the Muddied Waters

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The autosomal dominantly inherited hamartoma polyposis syndromes comprise juvenile polyposis syndrome or juvenile polyposis coli (JPS; OMIM 174900), Cowden syndrome (CS; OMIM 158350), Bannayan-Ruvalcaba-Riley syndrome (BRR; OMIM 153480), and Peutz-Jeghers syndrome (PJS; OMIM 174900). The molecular basis of these syndromes has remained elusive until recently, in part because of the often subtle clinical distinctions among them. Since the risk of organ-specific cancers in each syndrome is different, a more reliable and objective means of differentiating among these syndromes would be desirable, such as one based on molecular diagnosis.

The first syndrome to yield to genetic analysis was CS, characterized by multiple hamartomas, including gastrointestinal hamartomatous polyps, and a high risk of benign and malignant neoplasms of the thyroid, breast, uterus, and skin (Eng and Parsons 1998). In 1996, CS was mapped to 10q22-24 (Nelen et al. 1996). The following year, germ-line mutations in *PTEN/MMAC1/TEP1,* encoding an ubiquitously expressed dual specificity phosphatase, were found in CS (see table 1; Li and Sun 1997; Li et al. 1997; Liaw et al. 1997; Steck et al. 1997). A few months later, germ-line mutations in *PTEN* were also noted in BRR, a congenital syndrome characterized by macrocephaly, lipomatosis, hamartomatous polyposis, hemangiomas, and speckled penis (Marsh et al. 1997*a*). From these data, one could conclude that CS and BRR are at least allelic and might even be one and the same syndrome along a broad spectrum. Buoyed by an early hope that *PTEN* would be the susceptibility gene for all inherited hamartoma polyposis syndromes, investigators rushed to their freezers to pull out samples from PJS and JPS cases. However, the identification of *LKB1/STK11,* mapping to 19p13.3, as the basis for PJS (see table 1; Hemminki et al. 1998; Jenne et al. 1998) demonstrated that this hopeful model was incorrect, but the etiology of JPS remained contentious.

Attention, therefore, turned to JPS. JPS is characterized mainly by the presence of gastrointestinal hamartomatous polyps and an increased risk of gastrointestinal malignancy. The diagnosis of JPS is made only if features classic for other syndromes are not present. Preliminary genetic data seemed more than suggestive: somatic data pointed to the existence of a putative locus for JPS, called *JP1,* at 10q22-24 encompassing *PTEN,* although fine structure mapping placed this locus centromeric to *PTEN* (Jacoby et al. 1997). These findings were sufficient to induce several groups to pursue *PTEN* as a candidate for *JP1,* with confusing results. Three studies, including one published in this issue of the *Journal,* comprising a total of 21 classic JPS families and 16 sporadic cases, were found not to have any germ-line *PTEN* mutation (Marsh et al. 1997*b*; Howe et al. 1998 [in this issue]; http://128.220.85.41:5002/MCGI/SEND1^WEBUTLTY(1378,1)/1674326758). In addition, the 10q22-24 region could be excluded as a putative JPS locus in 15 of these families by linkage analysis (Marsh et al. 1997*b;* Howe et al. 1998). Recently, three unrelated "JPS" cases were reported to harbor germ-line *PTEN* mutations (Olschwang et al. 1998). Interestingly, the adult male patient (G116) with gastrointestinal hamartomatous polyps also had laryngeal carcinoma and a heterogeneous thyroid nodule. Clinically, the presence of hamartomatous polyps, laryngeal carcinoma, and a heterogeneous thyroid nodule is highly suggestive of CS. Unfortunately, insufficient clinical detail, especially the dermatologic examination, was reported. The two children (G796 and G710), respectively diagnosed at ages 14 and 3 years (current age 10), were reported not to have manifestations of CS or BRR (Olschwang et al. 1998). CS carries an age-related penetrance: 90% by the age of 20 years and well under 10% below age 15 years (Nelen et al. 1996). Indeed, initial linkage studies excluded all cases under the age of 20 years, because penetrance is known to be low under the age of 20 years (Nelen et al. 1996). Because of the presence of germ-

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Table 1

Genes Involved in the Inherited Hamartomatous Polyposis Syndromes

Syndrome	Localization	Susceptibility Gene	Reference
CS	10q23.3	*PTEN*	See text
BRR	10q23.3	*PTEN*	Marsh et al. (1997*a*)
	Other	?	
PJS	19p13.3	*LKB1/STK11*	See text
	19q13.4?	?	Mehenni et al. (1997)
JPS	18q21.1	?	Howe et al. (1998)
	6q?	?	Thomas et al. (1996)
	Others	?	

line *PTEN* mutations, these two children may eventually develop other features that could be clinically diagnostic of CS, and they should not be diagnosed as JPS until it is clear that they lack other features typical of CS as adults. A similar theme is underscored by another study that ascertained a family with "JPS," but with germ-line *PTEN* mutation, R334X (Lynch et al. 1997). On further clinical investigation, the affected members of this family were found to have macrocephaly, small bowel hamartomatous polyps, small intestinal carcinoma, and skin lesions typical of CS. In addition, the affected adult had small intestinal adenocarcinoma. The presence of classic clinical features that agree with the diagnostic criteria of the International Cowden Consortium (Eng and Parsons 1998) and the presence of a germ-line *PTEN* mutation argue convincingly for a single, unifying diagnosis of CS for this family.

Because phenotypic features may be shared by several hamartoma syndromes and the clinical diagnosis is not straightforward, only physicians with extensive experience with these disorders may be able to distinguish reliably among these disorders. Diagnosis is even less straightforward if it is a diagnosis of exclusion, as is the case for JPS. It is important to distinguish the various hamartoma syndromes, as the predisposition to cancer or the types of cancers might be quite different among them. Therefore, we propose that the presence of a germ-line *PTEN* mutation is a useful molecular diagnostic sign for CS or BRR. If a "JPS" patient is found to harbor an occult germ-line *PTEN* mutation, the clinician should consider CS or BRR as the diagnosis and should monitor the skin, thyroid, breast, and uterus for cancer development.

What of the inherited hamartoma syndromes that are characterized by germ-line *PTEN* mutation? Depending on the study one reads, the *PTEN* mutation frequency ranges from a low of ~10% (Tsou et al. 1997) to a high of ~80% (Liaw et al. 1997; Marsh et al. 1998), with varying frequencies in between (Lynch et al. 1997). All of these studies state adherance to the International Cowden Consortium operational diagnostic criteria for CS (Eng and Parsons 1998). However, on close scrutiny, the studies that ascertain CS through strict adherence to these criteria have reported the highest mutation frequency (Liaw et al. 1997; Marsh et al. 1998). That these studies have been the most reproducible suggests that the operational criteria are robust. Similarly, approximately half of all BRR cases ascertained by the minimal features of congenital macrocephaly, lipomatosis, and speckled penis (with or without intestinal hamartomatous polyposis) have been found to carry germ-line *PTEN* mutation (Marsh et al. 1998). There are at least two "JPS" patients described to have constitutional deletion encompassing 10q23 and *PTEN* (Jacoby et al. 1997; Tsuchiya et al. 1998). The patient described by Jacoby et al. (1997) also had dysmorphic features and microcephaly. It is unclear whether this patient can really be clinically classified as classic JPS. The second patient described by Tsuchiya et al. (1998) clearly has the clinical features diagnostic for BRR. Corroborating this, this patient had a deletion 10q23.2-23.33, a mere 5 cM encompassing *PTEN* (Tsuchiya et al. 1998). This case is reminiscent of that of Arch et al. (1998), who first described a BRR case in the setting of a 10q deletion that encompasses *PTEN*. In summary, therefore, finding a germ-line *PTEN* mutation is molecular evidence for the diagnosis of CS or BRR. The absence of an identifiable *PTEN* mutation is, for now, nondiagnostic. Much work still needs to be done in the field of inherited hamartoma syndromes before a comprehensive molecular classification can be attained. The work of Howe et al. (1998) localizing a JPS locus to 18q is yet another step toward this goal.

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References

Arch EM, Goodman BK, van Wesep RA, Liaw D, Clarke K, Parsons R, McKusick VA, et al (1997) Deletion of *PTEN* in a patient with Bannayan-Riley-Ruvalcaba syndrome suggests allelism with Cowden disease. Am J Med Genet 71: 489–493

Eng C, Parsons R (1998) Cowden syndrome. In: Vogelstein B, Kinzler KW (eds) The genetic basis of human cancer. McGraw-Hill, New York, pp 519–526

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, Ringold JC, Summers RW, Mitros FA, Nishimura DY, Stone EM (1998) A gene for familial juvenile polyposis

maps to chromosome 18q21.1. Am J Hum Genet 62: 1129–1136 [in this issue]

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-i, Friedel W, Loff S, Jeschke R, Müller O, et al (1998) Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. Nat Genet 18: 38–44

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

Li J, Yen C, Liaw D, Podsypanina K, Bose S, Wang S, 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 PLM, 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

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 syndrome, and juvenile polyposis. Am J Hum Genet 61:1254–1260

Marsh DJ, Coulon V, Lunetta KL, Rocca-Serra P, Dahia PLM, Zheng Z, Liaw D, et al (1998) Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, 2 hamartoma syndromes with germline *PTEN* mutation. Hum Mol Genet 7:507–515

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

Marsh DJ, Roth S, Lunetta K, Hemminki A, Dahia PLM, Sistonen P, Zheng Z, et al (1997*b*) Exclusion of *PTEN* and 10q22–24 as the susceptibility locus for juvenile polyposis syndrome (JPS). Cancer Res 57:5017–5021

Mehenni H, Blouin JL, Radhakrishna U, Baradwaj S, Baradwaj K, Dixit VB, Richards KF, et al (1997) Peutz-Jeghers syndrome: confirmation of linkage to chromosome 19p13.3 and identification of a potential second locus on 19q13.4. Am J Hum Genet Suppl 61:A74

Nelen MR, Padberg GW, Peeters EAJ, Lin AY, van den Helm B, Frants RR, Coulon V, et al (1996) Localization of the gene for Cowden disease to 10q22-23. Nat Genet 13: 114–116

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

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

Thomas HJW, Whitelaw SC, Cottrell SE, Murday VA, Tomlinson IPM, Markie D, Jones T, et al (1996) Genetic mapping of the hereditary mixed polyposis syndrome to chromosome 6q. Am J Hum Genet 58:770–776

Tsou HC, Teng D, Ping XL, Broncolini V, Davis T, Hu R, Xie X-X, et al (1997) Role of *MMAC1* mutations in early onset breast cancer: causative in association with Cowden syndrome and excluded in *BRCA1*-negative cases. Am J Hum Genet 61:1036–1043

Tsuchiya KD, Wiesner G, Cassidy SB, Limwongse C, Boyle JT, Schwartz S (1998) Deletion 10q23.2-10q23.33 in a patient with gastrointestinal juvenile polyposis and other features of a Cowden-like syndrome. Genes Chromosom Cancer 21: 113–118