INVITED EDITORIAL
Classification of Familial Adenomatous Polyposis: A Diagnostic Nightmare

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How dramatically things have changed in 10 years! In 1988, we described a colon cancer–prone family with a tendency to form small, right-sided adenomas (Lynch et al. 1988). We proposed that the family represented either hereditary nonpolyposis colorectal cancer with a previously undescribed precursor lesion or a new colon cancer syndrome. (We were wrong on both counts.) Later, emphasizing the morphology of the small adenomas, we proposed the term hereditary flat adenoma syndrome (another wrong idea) (Lynch et al. 1992). Investigators from the University of Utah made the critical link to the *APC* gene, recognized that mutations nearer the 5′ end of the gene were associated with the phenotype, and supplied the appropriate name: attenuated familial adenomatous polyposis (AFAP) (Spirio et al. 1992, 1993). Now, Soravia et al. 1998 (in this issue) add new evidence for genotype-phenotype correlations and extend the mutational spectrum associated with the attenuated phenotype.

Soravia et al. (1998) describe three classes of *APC* mutations in kindreds with an attenuated phenotype. First, there are four families with mutations in exon 4 that generate truncated proteins prematurely terminated at nucleotides 551 (three families) or 487. Individuals with these mutations tend to form dozens to hundreds of adenomas, but the range is broad (2 to >500), and in some patients the adenoma phenotype resembles that of "classic" familial adenomatous polyposis (FAP). (This is similiar to our experiences with these types of families.) Upper gastrointestinal manifestations are common, again paralleling our experience. Second, there are two families with truncating mutations in exon 9, one resulting in premature termination at nucleotide 994 and one at nucleotide 1014. Individuals with these mutations have fewer adenomas (1–150) and no apparent upper gastrointestinal manifestations. Finally, there is a remarkable family with a mutation near the distal end of the *APC* gene, resulting in termination at nucleotide 6218. The four family members known to carry this mutation have manifested as many as 36 adenomas; two have adenomas in the upper gastrointestinal tract, and none of the four has developed a colorectal carcinoma (CRC). This family might best be classified as very attenuated FAP, and its paucity of adenomas and apparent low risk for CRC make one wonder how much the mutation found in this family contributes to apparently sporadic CRC in the general population. In all groups, age at diagnosis was older than for classic FAP, and right-sided adenoma predominance with rectal sparing was seen in at least some individuals.

We know now that individuals carrying germ-line mutations of the *APC* gene might have anywhere from one to thousands of adenomas and that the lifetime risk for CRC ranges from low to nearly 100%. The phenotypic range forms a continuous spectrum, and it is probably arbitrary to divide the spectrum into profuse polyposis, classic polyposis, sparse polyposis, attenuated polyposis, and very attenuated polyposis. How many adenomas can there be, for example, before attenuated polyposis becomes sparse polyposis? Arbitrary though the divisions may be, they are also necessary, because estimates about the lifetime risk for CRC will influence the decision whether to proceed with prophylactic colectomy and how colectomy should be performed, and estimates of the expected incidence and location of extracolonic manifestations will influence surveillance strategies.

How, then, can we best subclassify FAP? Certainly, genetic analysis will play a role, given the genotype-phenotype correlations described above and other work (reviewed by Soravia et al.) correlating specific mutations with other phenotypic features, such as desmoid tumors and congenital hypertrophy of retinal pigment epithelium. Additional descriptive studies correlating mutations with phenotype will undoubtedly appear, further extending our ability to predict clinical findings on that basis. We doubt, however, that analysis of *APC* mutations alone will allow definitive subclassification. There are just too many phenotypic variations, even within families carrying identical mutations. The role of

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modifier genes and the effect of environmental influences remain to be elucidated. A combination of clinical judgment and genetic analysis is called for.

We think there are two important messages to convey: First, clinicians must be aware of the broad range of clinical features that FAP can present. AFAP should be considered when fewer adenomas are present (<100 in at least some family members) and when they tend to be right sided. Second, classically described surveillance and prophylactic measures do not apply to all cases of FAP. In the management of patients that we classify as AFAP, we recommend colonoscopy with polypectomy. When the total number of colonic adenomas is too numerous to follow with colonoscopy and polypectomy, particularly when the adenomas are located in the cecum, we recommend prophylactic subtotal colectomy with continued follow-up of the rectal segment by endoscopy. We also suggest early upper endoscopy be performed in these families, in that multiple fundic gland polyps have *preceded* the finding of pathology in the colon in the relatively large number of our patients with AFAP. Although fundic gland polyps commonly occur in the general population and are considered to be benign, we find them to be a sensitive marker of mutation carriers in the AFAP setting. There are rare reports of dysplasia in fundic gland polyps of AFAP patients (Zwick et al. 1997), something we have observed as well. These findings may represent gastric dysplasia coincidentally involving a fundic gland polyp, but clearly the stomach bears watching in AFAP. We should also mention the potential for duodenal adenomas and periampullary cancer, but we emphasize that we do not know whether the periampullary cancer risk in AFAP approaches that of classical FAP. We should be on the lookout for desmoids, although they were not previously reported in AFAP. Of course, we should continue the search for any of the extracolonic cancers that characterize the classical form of FAP.

Genotype-phenotype interactions in FAP are complex, but if a mutation known to be associated with an attenuated phenotype is documented, the clinician must look for clinical evidence of attenuated phenotype. If clinical findings support the diagnosis, surveillance and management guidelines should be modified accordingly.

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