Genetic Testing and Counseling in Familial Adenomatous Polyposis

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Testing for adenomatous polyposis coli (APC), the gene responsible for familial adenomatous polyposis (FAP), can now be offered to family members in FAP kindreds. With the availability of this test, genetic counseling has become a crucial tool for helping FAP patients and their relatives understand the syndrome and its implications and for assisting at-risk individuals in making informed decisions about whether or not to undergo genetic testing. Genetic counseling can occur at several time points: when FAP is diagnosed, when an FAP patient is considering reproductive options, when a patient is deciding whether to have his or her children screened, and when an at-risk person is considering genetic testing.

Introduction

Over the past decade, we have made major discoveries about the molecular genetic basis of colorectal cancer, including the identification of genes that cause certain colorectal cancer syndromes [1-4]. There is little doubt that these discoveries will lead not only to a better understanding of etiology but also to improvements in the clinical management of colorectal cancer patients and their families.

One of the best examples of how basic research has made the transition to clinical application is in familial adenomatous polyposis (FAP). As a result of the discovery and characterization of the gene for FAP, predictive genetic testing can now be offered to family members in FAP kindreds [5]. However, the new technology carries an important responsibility for the clinician to help at-risk individuals who may choose genetic testing to understand the implications of the test. We will briefly review the genetics of FAP, and discuss the various issues related to the genetic counseling and management of FAP patients, at-risk persons, and their families. Our paper represents a body of experience drawn from work with families in the FAP registry at The Johns Hopkins Hospital [6]. The Hopkins registry, which originated in 1973, has followed hundreds of FAP patients from over 300 families, many of them large and multigenerational. We will present several case reports to illustrate the breadth of the issues that may arise in the context of predictive genetic testing for FAP.

Genetics of FAP

The clinical features of FAP have been well documented [7-9]. As its name implies, familial adenomatous polyposis is a condition characterized by numerous adenomatous polyps (100) in the colon, which exhibits autosomal dominant inheritance in families. This means that affected persons are heterozygous, such that each offspring of a patient with FAP has a 50% chance of inheriting the disease gene. The gene responsible for FAP is known as APC (for adenomatous polyposis coli) and is located on chromosome 5q21 [1-2,10].

Mutations of the APC gene have been found in patients with FAP (eg, 2,11). These are often insertions, deletions, and nonsense mutations that lead to frameshifts and/or premature stop codons in the resulting transcript of the gene. It is not yet clear how the subsequent truncated protein product causes adenomas to form. Capitalizing on the nature of these mutations, however, has led to the development of a molecular genetic test for FAP [12]. Unlike genetic linkage analysis, this test is useful with spontaneous, or "new mutations" (the first occurrence of FAP in a kindred), which may account for as many as one-third of incident cases [7-9].

Genetic and Clinical Heterogeneity

Recent evidence suggests that there is genetic heterogeneity of FAP. Several kindreds have been described that do not appear to be linked to the gene region on chromosome 5q [13]. Also, in some
FAP patients, there has been an apparent inability to detect APC mutations [12,14]. On the other hand, clinical variability of FAP has been manifested by the appearance of the adenomas in some families that do have an APC mutation. A variant entity of FAP with attenuated polyps has been called the hereditary flat adenoma syndrome [15,16], and in the reported kindreds appears to be due to mutations in the APC gene. Other workers have suggested, however, that diminutive adenomas will progress to larger, ordinary adenomas [17].

**Conventional Management of FAP**

Individuals who inherit a mutant APC gene have a very high likelihood of manifesting colonic adenomas; penetrance has been estimated to be over 90% [7-9]. The age at onset of adenomas in the colon is variable. Cumulative age-at-onset curves suggest that by age 10 years, only 15% of FAP gene carriers manifest adenomas; by age 20, the probability rises to 75%; and by age 30, 90% will have presented with FAP [7-9,18]. Without any intervention, most persons with FAP will inevitably develop colon or rectal cancer by 40 years of age. Thus, the medical goal in patients with FAP is to prevent colon cancer. Conventional management of persons at 50% risk of developing FAP has been to initiate annual colon surveillance by flexible sigmoidoscopy in late childhood and to perform subsequent colectomy when numerous polyps are present [19,20]. While it is not unusual to find FAP patients under age 12 who have dozens of polyps, colon cancer has been reported in children as young as 10 years of age [7-9]. Under no circumstances, however, is preventive colectomy indicated in FAP patients prior to the appearance of polyps.

**Contexts of Genetic Counseling**

Genetic counseling of FAP patients and their family members can occur in several contexts: at the time of diagnosis of FAP, at the time that an FAP patient is considering reproductive options, at the time that the FAP patient is having his or her children screened, and at the time that an at-risk person is considering genetic testing. In the following sections, each of these contexts will be discussed in light of new information and risks that can be conveyed during counseling at that particular time.

**When FAP Is Diagnosed**

This is the most common, conventional context in which FAP patients are told about the condition and its genetic implications. Not only are these patients coping with the disease and its medical implications, they are also told that it is hereditary and that their offspring may inherit the condition. For newly diagnosed patients, this can be the most stressful time, as they deal with the clinical sequelae, medical tests, and eventual surgery. Often, patients with "new mutations" may have been diagnosed when symptoms and possibly colon or rectal cancer have presented. Thus, they may not be ready to absorb the genetic implications of FAP until they have dealt with the requisite medical procedures. Genetic counseling of newly diagnosed FAP patients and their families is essential. Since many patients may be learning for the first time about the hereditary nature of FAP, referral to a clinical geneticist or genetic counselor is optimal, although we have observed that this often does not occur in practice. The genetic counselor obtains detailed information about the family history, including health and cancer histories of blood relatives; family structure; and social support within and outside the immediate family. Once this information has been collected, pedigrees are drawn and recurrence and other risks assessed. Genetic counseling generally serves two functions: (1) to help the patient and family understand medical and genetic information about FAP, and (2) to provide emotional and psychological support as the family copes with the new information and burdens that such information can impose. This process is best accomplished by a series of discussions over time. Because so much has been learned about the genetic basis and management of FAP, patients can be given reasons to be hopeful about future prospects in prevention and treatment of this condition.

**When Starting or Continuing a Family**

Increasingly more often, FAP patients are being diagnosed in late childhood or adolescence [7,20]. When such patients mature and decide to start their own family, the genetic counselor or health professional needs to review and discuss with both the patient and his or her partner many of the issues related to inheritance and the latest technological developments. Specific issues to be reviewed include the mode of inheritance of FAP, the recurrence risk for offspring, and the fact that the risk of FAP for each offspring is independent of the others.
After a careful, sensitive exploration and discussion of the goals, values, and wishes of the couple, reproductive options can be sifted, including the feasibility of prenatal genetic diagnosis, adoption, and artificial insemination. Prenatal genetic diagnosis of FAP is a technically feasible option, but neither has ever been performed, to the authors’ knowledge. Anecdotally, during the course of pregnancy, several couples have inquired about prenatal genetic diagnosis, but after thinking through the consequences (ie, what would they do should the gene test indicate that the fetus had inherited the mutant APC gene?), this option was not elected. These experiences underscore the importance of careful, thoughtful discussion of all the issues. A related, but different situation occurs when a couple may already have one or two children and wish to have more, but the decision depends on whether those already born have inherited the FAP gene. Couples may have different, often valid rationales for seeking this information about children who may be quite young and for whom intervention may be years away. These reasons may include burden of caretaking, insurance coverage, or financial obligations for which the couple may want to appropriately plan.

**When Having Offspring Screened**

In the absence of predictive genetic testing, genetic counseling can be useful to review with children at the time that their regular colon screening regimen begins. As described below [21], we have found that children may have an incomplete understanding of the reason for their medical tests. Thus, it is helpful to talk to the children in terms that they can understand about what FAP is and what it can mean if polyps are found.

**When Predictive Gene Testing is Requested**

Perhaps the most important development in the management of families with FAP is the use of predictive gene testing. In this context, both children and adults at 50% risk can benefit from genetic testing because of the reduction in uncertainty regardless of test outcome, modifications in screening guidelines for those who do not have the mutant gene, and increased compliance with screening regimens among those who do have the gene [18,21].

Genetic test results can change risks for FAP from the a priori value of 50% to essentially 0 or 100%. We have modified recommended follow-up screening based on genetic test outcomes [22], as summarized in Table 1. Presymptomatic genetic testing removes the necessity for annual screening of at-risk individuals who do not have the gene, and likely improves compliance in those who do. For the majority of persons who are APC gene-positive, it is very likely that colon adenomas will develop. However, surgical removal of polyp-free colons is not indicated even in individuals who are gene-positive. The timing of surgery should depend on the number of polyps found in the colon. There is a relatively long time span from the average age of polyp onset (15 years old) to the average age of colon cancer in FAP (35 years old), so that endoscopic surveillance is the preferred management following the genetic test in children.

There is hope that nonsurgical intervention in FAP may be possible. Recent studies have shown that the non-steroidal anti-inflammatory drug sulindac reduces the number and size of polyps in FAP patients [23]. It is not yet known, however, whether administration of sulindac will prevent or delay the onset of polyps.

Presymptomatic genetic diagnosis of FAP in at-risk individuals has been feasible with linkage [18] and direct detection [22] of APC mutations. These tests require a small sample (10 cc) of blood, and the lymphocyte DNA is tested. With linkage analysis, ancillary family members need to be sampled, and more than one affected individual is needed. With direct detection, the specific mutation must be known, but other family members’ blood samples are not required. The latter method is useful for testing at-risk offspring of FAP patients with new mutations.

The swift pace of molecular genetic technology has recently enabled a simpler assay for the truncated protein product using in vitro transcription of the APC gene, or allele-specific expression to identify promoter or splice mutations by reduced levels of APC transcripts [12]. Approximately 80% of APC mutations can be detected by this method. This new technology considerably enhances the feasibility of testing at-risk individuals without requiring DNA from family members affected with FAP.

**Issues Raised by Genetic Testing**

Genetic counseling is an important component of the gene testing protocol. Our research team was among the first to offer predictive genetic testing for FAP shortly after the APC gene was discovered. In each case, genetic testing was offered to individuals from families in The Johns Hopkins FAP Registry in which the specific APC mutation was known and characterized [21-22]. The cases
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The following cases illustrate the variety of concerns and circumstances that can be found when genetic tests are offered in FAP families:

**Case 1: Testing Offspring of a FAP Patient**

A 38-year-old woman contacted the Johns Hopkins FAP Registry requesting information about the availability of genetic testing for her three children, each of whom had a 50% risk of developing FAP. The woman explained that her husband, who was affected with FAP, died 8 months ago as a result of inoperable desmoid tumors, known to be associated with FAP [7-9].

The woman also reported that one of her children, a 7-year-old son, had never had a colon examination, whereas the other two children had recently been examined. No polyps were found in the 14-year-old son, but the 10-year-old daughter was found to have several colon polyps. Since the presence of multiple polyps is clinically diagnostic of FAP, the genetic counselor explained that it would be possible to perform predictive gene tests on the at-risk sons if a mutation could be detected in a blood sample from this affected daughter.

After discussing and thinking through the implications of genetic testing (including test specificity) with the genetic counselor, the woman decided to have her daughter's blood tested. An APC gene mutation was identified, providing a molecular diagnostic confirmation of the flexible sigmoidoscopic finding. The woman and her two sons then met with a genetic counselor, who talked directly with them about what FAP is and what the genetic test results could mean. The level of communication differed because of the boys' ages. Age-appropriate materials were used to stimulate discussion. Both boys elected to have the test, indicating a wish to know for certain whether they had FAP. The test revealed that both boys did not have the FAP gene. These results not only eliminated the need for the boys to have annual sigmoidoscopies but also provided the family with a welcome sense of relief.

**Case 2: Testing Members of an Affected Kindred**

Two sisters, 21 and 22 years old, were identified as being at risk for FAP and were contacted by the team. Their father and many other family members were affected with the condition, and the APC mutation had already been identified in this kindred. The young women had never had colon examinations and were reluctant to undergo this type of procedure. They did not fully understand that the genetic nature of the condition made colon screening necessary.

After the women were counseled about their risk for polyposis and colon cancer, they did choose to participate in a research study that included concurrent flexible sigmoidoscopy and genetic testing. We found that it was the promise of a definitive genetic test that convinced these women to have the flexible sigmoidoscopic examinations. The younger sister was found to have colon polyps, precluding the need for genetic testing. These sigmoidoscopic findings were initially quite upsetting to this young woman. She was counseled immediately following sigmoidoscopy, and medical recommendations (including surgery) were made by the gastroenterologist. Several conversations with this woman followed her initial visit, to help her adjust to the diagnosis of FAP. The older sister was found not to have any colon polyps, and she elected to proceed with APC gene test. Her test result was negative.

Each woman has a young son, which engendered further counseling. The son of the younger, affected sister has a 50% risk of FAP, and the FAP risk for the son of her sister is essentially 0.

**Case 3: Confusion About Negative Test Results**

We have encountered several incidents outside of our registry's activities in which the incorrect use of genetic testing for FAP by clinicians resulted in confusion within FAP families. Whenever possible, a family member affected with FAP must undergo genetic testing first in order to identify the specific mutation. When no affected family member is available, genetic testing of at-risk family members is not always useful. A positive result in an at-risk family member is a true-positive result. However, a negative result could be a false-negative due to the fact that the gene mutation is undetectable in approximately 20% of FAP families.

One reported incident involved genetic testing of an at-risk teenager. This child's father had died as a result of FAP-related colon cancer, and there were no other living affected family members. The teenager had undergone genetic testing, and the laboratory report stated "no gene mutation found." The physician, however, reported the result to the family as "negative," and did not tell the family that this result could be a false-negative. They consequently planned to discontinue colon screening. We later counseled the family and explained that the child was still at risk of developing FAP. We recommended that the child continue colon screening.

Components of Genetic Counseling
Genetic counseling must accompany genetic testing, because of the implications for family members and for reproductive decision-making. Patient information pamphlets on FAP (our registry at Johns Hopkins, along with other FAP registries around the world, has developed such materials), genetic tests [24], and other age-appropriate visual aids (for an example, see reference 25) are very useful adjuncts to genetic counseling. A typical genetic counseling session should include the following components [21]:

**Education**—Genetic counseling should first educate the family about the clinical and management aspects of FAP, its hereditary nature, the risks of cancer, the consequences of receiving gene-positive or -negative test results (Table 2), and the recommended screening guidelines for each possible test outcome.

**Exploring Family History and Experiences**—Genetic counseling must also include an exploration of specific issues related to the family history and experiences with FAP. These experience can span many generations and can include close personal involvement with relatives who have had cancer and/or surgical interventions. Family relationships can be profoundly affected by issues such as guilt and blame, and personal and familial identity may be strongly linked to FAP status. Other issues include the denial of disease risk or stigmatization of cancer within the family, and the acceptability, convenience, or affordability of screening regimens. Thus, genetic testing is imbued with meaning for certain patients far beyond its ostensible function as a simple determinant of genetic status. An understanding of the patient's perspective is crucial so that it can be taken into account when assisting him or her adjust to genetic test results.

**Exploring Perception of Risk**—Another important aspect of counseling is an exploration of the perception of risk and its meaning, as well as the anticipated meaning of any test results. With parents of at-risk minor children, time should also be devoted to discussing how and when the test results and risk will be communicated to the children. In certain countries, employability or loss of insurability (life or health) is a risk, although its magnitude is unknown at present. The decision to undergo genetic testing should be made freely by the at-risk person after careful consideration of the consequences of genetic testing (described below). It may also be useful to employ a consent form that outlines the meaning of test results and the consequences of the test. **Disclosure of test results**, which can typically occur 2 weeks to 1 month later, provides another opportunity to meet with the at-risk individual and explore the meaning of the test and to discuss in a more meaningful manner the likely follow-up regimen and the risks to future offspring. Because of the implications of genetic testing, it is recommended that results be disclosed to the tested individual by the health professional in person.

**Follow-up Session**—For persons who test positive for the FAP gene, we strongly recommend a third follow-up session (either by telephone or in person), in which the patient is allowed a second opportunity, free from the initial emotional reaction to the test result, to ask questions about clinical management. This follow-up visit also permits the clinician an opportunity to determine whether referral to a mental health professional for additional support is indicated.

**Consequences of APC Gene Tests**

Some potential consequences of APC gene test results, negative and positive, are listed in Table 2. As can be seen, a number of issues should be discussed with individuals who are to be genetically tested. We have found that the gene test is imbued with meaning beyond the determination of gene status in families who choose gene testing. The at-risk patient has preformed, well-entrenched conceptions of what having FAP or colorectal cancer entails, and family relationships and identity may be strongly linked with disease or gene status. In particular, if the tested individual is a minor, the parents need to understand the consequences for their child, and that counseling a child in the context of FAP gene testing requires great sensitivity to the child's level of understanding and fears [21]. Parents' reports of what their child has been told may not be accurate. We have found that children can have little knowledge of FAP or have developed beliefs about FAP that have no basis in fact, to the surprise of their parents. Careful, considerate discussion with the parents and directly with the child are important components of counseling. When disclosing a child's test results, it is recommended that the parents be told first, without the child present. This allows both the medical implications and emotional reactions to the results to be discussed, along with options for how to disclose the information to the child [21].

In our experience, we have found that, regardless of the outcome of genetic testing, reduction of uncertainty for at-risk persons (and their parents) and increased compliance with colon screening
recommendations are important benefits. Individuals who have been tested have described a variety of emotional reactions to presymptomatic testing. These include relief and happiness in response to negative test results, and relief, sadness, or distress in response to positive test results. Parents of tested children have described feeling shocked, saddened, or relieved by their children's test results. We have not found serious adverse psychological reactions, but because of the emotional consequences, it is important for the health-care professional to understand these issues when offering the test.

Conclusions

New research developments in the molecular genetics of FAP have led to the feasibility of presymptomatic genetic testing for this condition. Although the traditional settings in which genetic information about FAP is given (at the time of diagnosis, starting a family, or having offspring screened) have been affected by this new knowledge, the most dramatic changes have occurred in the context of predictive genetic testing. Genetic test results have clinical implications for management: Conventional colon screening guidelines can be modified in light of test results such that those at high-risk for FAP (e.g., gene-positive individuals) will be identified for more vigilant surveillance of colonic and extracolonic tumors and those at low-risk (gene-negative patients) will be advised to reduce the number of colon examinations. Genetic counseling is an important addition to the array of changes in the management of FAP. Counseling is of particular value in helping children at risk understand the implications of genetic testing.

References:

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