



# AMGP "M.U.G."

## "Monthly Update in Genetics"

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### Hereditary Colorectal Cancer

Among the hereditary cancer syndromes the breast-ovarian cancer syndrome (**BRCA1/2** genes: see MUG 10/2002) has received the most attention recently. The advent of direct-to-patient marketing in Denver and Atlanta has increased the prominence of this disorder. Reflecting this is the fact that a majority of patients referred to the UCHSC Hereditary cancer clinic are being evaluated for evidence of the hereditary breast-ovarian cancer syndrome. In spite of the relative success in increasing awareness of this syndrome, the recognition of other cancer syndromes may be lagging.

**Colorectal (CRC)** cancer affects approximately 150,000 persons (breast cancer ~180,000) and causes ~55,000 deaths (breast cancer ~45,000) annual in the United States. The lifetime risk of **CRC** is estimated to be ~2-3% by age 70 in the general population. **From a hereditary standpoint the family history provides important risk-stratification information.** Individuals with a **single affected first-degree relative** (parent, sibling, offspring) have an **8% risk of CRC**; having just **two affected first-degree relatives** elevates this risk to **17%**. As with other cancer syndromes, the collection and study of large pedigrees affected by CRC has led to the identification of the genes responsible for the Mendelian forms of the disease, estimated to account for ~5-10% of all colorectal cancer.

These syndromes include two, relatively more common syndromes (**Familial Polyposis Coli** and **Hereditary Nonpolyposis Colorectal Cancer syndromes**), and other rarer syndromic forms of disease: **Cowden's disease**, **Familial Juvenile Polyposis**, and the **Peutz-Jeghers** and **Bannayan-Ruvalcaba-Riley** syndromes.

In the case of **Familial Polyposis Coli**, this entity has been recognized for decades due to the remarkable phenotypic appearance of the colon. This condition is inherited in an autosomal dominant pattern due to mutations in the **adenomatous polyposis coli (APC)** gene. Affected individuals present with multiple colonic adenomas that typically develop in adolescence and degrade into malignant tumors by the 5<sup>th</sup> or 6<sup>th</sup> decade. Even with conventional chemotherapeutic approaches the disease is uniformly fatal as the large number of polyps (100s-1000s) present in the colon portends the development of multiple CRCs.



Example of colonic mucosa extensively covered by polyps

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Colorectal Cancer Syndromes:

Familial Polyposis Coli Syndrome

Mutations leading to Truncated Protein Products						
Protein	→	Ser	Ser	Leu	Asp	Arg Ile →
RNA	→	UCU	UCG	CUU	GAU	CGA AUU →
DNA	→	TCT	TCG	CTT	GAT	CGA ATT →
Above: Normal DNA ≠ RNA ≠ Normal length protein						
Below: Results of insertion/substitution of nucleotides ≠ Truncated protein product						
Insertion of Alanine	→	TCT	TCG	<b>ACT</b>	<b>TGA</b>	Shortened/Truncated Protein
Point Mutation	→	TCT	TGG	CTT	GAT	<b>TGA</b> Protein
	→	Ser	Ser	Leu	Asp	<b>STOP</b>

The insertion of a single nucleotide can "shift" the reading frame (which reads nucleotides in groups of 3 called codons). Sometimes the shift in reading frame introduces a new stop codon that results in a shortened protein. Alternatively, a nucleotide can be changes (in this example from a C to a T which changes the CGA Arginine codon into a TGA stop codon. Again the protein product is shorter.

### PRACTICE SAFE GENETICS :

The intent of this newsletter is to increase your familiarity with clinical genetics. Genetic evaluations and testing raise many issues and are often most appropriately addressed in a genetics clinic setting. Please feel free to contact me with any clinical questions that arise as you care for your patients.

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Chemopreventive strategies with cyclooxygenase inhibitors (celecoxib and sulindac) appear to have efficacy in causing some polyp regression and slowing the development of new polyps. Ultimately, however a prophylactic subtotal colectomy is necessary to prevent the development of CRC. The timing of this surgery is often dictated on the basis of repeated colonoscopic screenings, that are often initiated in the pre-teenage years.

Because of the severity of the disease and the fact that colon changes occur in late childhood, **careful screening of at risk patients is necessary.** Genetic counseling and genetic testing can be employed to identify which persons in a given family are actually at risk for having germline APC mutations; and who, therefore needs to participate in these regular screenings. A 1997 NEJM study (*NEJM 1997;336:823-27*) reviewed the results of 177 patients who were tested for mutations in the APC gene. The physicians ordering the tests included surgeons, internists, and family practitioners. There are at least two points worth discussing here about this study. The first is that the “genetic test” used was a **protein-truncation** test. This test is based on the fact that the majority of mutations in the **APC** gene **result in a shortened (or truncated) protein.** As you might predict, many of these mutations involve small insertions/deletions of nucleotides in the DNA that shift the reading frame for protein translation (**frameshift mutations**) and cause the protein to be shortened. The shorten protein migrates differently and is readily detectable when compared to the normal protein. This concept is illustrated to the below. **Recognize that this “genetic” test is not a direct DNA test, but instead is a test of the phenotype (in this case the protein) resulting from a change in the DNA.**

The second message from this study is that in reporting the results of the genetic testing to the patients in this study in **~31% of the cases the physician reporting the results incorrectly interpreted the results and gave the patient information that was partially or wholly incorrect.** These physicians were informed enough to recognize the disorder, understand that genetic testing was available, and then were able to order the test: yet they were unable to interpret the results correctly 30% of the time. The most common mistake was to interpret a “negative” test result as being a “true negative” result when the mutation in a given family had not yet been

discovered.

Selecting the appropriate individual to test in a family (for cancer and many other genetic diseases) can be critical. Internists, who are not generally focused on approaching diseases from a family-based approach, need to consider fully the family pedigree. The **APC protein truncation** test from the NEJM article had a sensitivity of 80%. This means that out of 10 families who *have APC* gene mutations causing FAP, one should expect 8 of these families to have abnormal protein truncation testing results. The 2 families with normal protein truncation tests, *still have FAP, it is just that their mutations do not lead to an obviously shortened protein (and thus the test is negative).*

Thus in an APC family where the protein truncation test has 1) been used in an affected individual and 2) given an abnormal result, this test can be used in other relatives at risk. However in the case of a family where the protein truncation test gives a normal result OR no affected person has been tested to date, the results of testing are harder to interpret. An asymptomatic relative could have a “normal” test result because he/she didn’t inherit a mutation OR because the mutation in that family is not detectable by protein truncation. In this second scenario the “normal” test result is best interpreted as “uninformative” because the **validity of the test in that particular family has not yet been determined.**

In 6% of Ashkenazi Jewish persons there is a DNA variation in the APC gene. By itself this variation (a thymine to adenosine change seems to have no functional effect. The Isoleucine residue (normally in that position) is altered to a lysine but no truncated or malfunctioning protein results. Interesting, the substitution of an A for a T creates a stretch of 8 adenoses in the DNA (see figure).

Colonic cells have a high turnover rate and the entire colonic mucosa is replaced every few days. Although DNA replication machinery has a high fidelity, the process of repetitively copying this section of 8 adenoses is ultimately prone to some degree of error. The opportunity to *introduce* a mutation somewhere along the DNA copying process means that carriers of this variant are at risk to create somatic mutations of their APC gene that may ultimately lead to cancers. The risk associated with this variant is not great, approximately **twice the CRC risk** in the general population. It does however provide an interesting example of how a germline harmless variant sets the

stage for an increased risk of an eventual “somatic” mutation. In a later edition of the MUG we will discuss **hereditary non-polyposis cancer** which also develops as the result of a germline change predisposing to future mutational events.

Somatic mutations in carriers of 11307K	DNA sequence											
	GCA	GAA	ATA	AAA	GAA	AAG	ATT	GGA	ACT	AGG	TCA	
	+A		A	+G	G to T					-G		
DNA sequence	GCA	GAA	ATA	AAA	GAA	AAG	ATT	GGA	ACT	AGG	TCA	
Amino acid	Ala	Glu	Ile	Lys	Glu	Lys	Ile	Gly	Thr	Arg	Ser	
Codon no.	1305	1306	1307	1308	1309	1310	1311	1312	1313	1314	1315	