ANALYSIS OF **APC MUTATION-NEGATIVE PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS**

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Colorectal cancer is the second leading cause of death among cancer patients with over 100,000 new cases diagnosed every year. It is estimated that 30% of all colorectal cancer cases stem from inherited factors. Familial adenomatous polyposis (FAP) is a rare colorectal cancer predisposition syndrome. The syndrome is characterized by hundreds to thousands of adenomatous colonic polyps by early adolescence. Underlying mutations in the adenomatous polyposis coli (APC) gene are found in 80-90% of the cases. Through studying FAP patients enrolled in the Hereditary Gastrointestinal Cancer Registry (HGCR), we are characterizing undetected mutations, often in the noncoding regions of APC, for this syndrome.

This project focuses on mutation discovery in mutation-negative patients from the registry with a diagnosis of polyposis, either classic FAP, an attenuated form called AFAP, or an unclassified polyposis. This study will allow further definition of the patients in the registry as well as develop a better understanding of the syndrome.

Research subjects were selected from the HGCR; there were 20 families with polyposis that were still mutation negative after clinical genetic testing of APC as well as MUTYH, mutations in which cause a phenotypically similar recessive condition MUTYH-associated polyposis (MAP). Analyses applied to these samples included the use of PCR to examine cDNA for splice defects, large deletion analysis by MLPA, allelic imbalance by TaqMan, sequencing of published mutation sites in two additional genes recently linked to polyposis (PolE and PolD1), and sequencing conserved transcription binding sites in those samples with allelic imbalance.

Currently, nine of the families were eligible for the TaqMan assay and six were determined to have allelic imbalance. On further analysis, it appears all six patients have two undocumented SNPs. If these SNPs fall within a conserved transcription binding site, they may be the causative mutation. The remaining patients require further analysis to determine the presence of allelic imbalance, as well as examining the relative transcription expression for transcript variants of APC in all patients.