Hereditary Nonpolyposis Colorectal Cancer, Type 1

Alternative Names
HNPCC1
Colon Cancer, Familial Nonpolyposis, Type 1
FCC1
COCA1
Lynch Syndrome I

WHO International Classification of Diseases
Neoplasms

OMIM Number
120435

Mode of Inheritance
Autosomal dominant

Gene Map Locus
2p22-p21

Description
Lynch syndrome is a hereditary non-polyposis colorectal cancer (HNPCC) characterized by the development of colon cancer at an early age, an excess of multiple primary colon cancer, and a predominance of proximal colon cancer. HNPCC accounts for about 1% of colorectal cancers, and its prevalence is of the order of 1:3000. Some populations, e.g. Finns, show a founder effect. HNPCC can be classified into two types: HNPCC-I and HNPCC-II. HNPCC-I is the site specific Lynch syndrome.

An International Collaborative Group on hereditary non-polyposis colorectal cancer (ICG-HNPCC) unified definitions and update criteria for HNPCC. Despite the availability of genetic tests for Lynch syndrome, family history remains the most important tool in the diagnosis of this disease. If the cancer onset starts in early age in an individual with Lynch syndrome, targeted cancer surveillance should be extended to all first-degree relatives at an early age.

Molecular Genetics
HNPCC is an autosomal dominantly inherited predisposition to develop colorectal cancer. HNPCC is defined as inactivating germline mutations in genes encoding components of the DNA mismatch repair (MMR) system. The single germline mutation in an MMR gene in an individual with HNPCC does not result in MMR deficiency. However, a second hit in the functional allele in a tumor does then result in loss of MMR. This leads to failure to repair errors introduced into DNA during DNA replication. Cells with defective MMR have very high rates of somatic mutation, and accumulate mutations randomly in many genes as well as non-coding DNA. Mutations may arise from inactivate tumor suppressor genes or activate cellular oncogenes, and therefore in turn give rise to cancer development.

To date germline mutations in four genes encoding components of the mismatch repair pathway have been shown to underlie HNPCC, these are: Homolog of MutS E. coli 2 (MSH2), Homolog of MutL E. coli 1 (MLH1), S. cerevisiae Postmeiotic Segregation Increased 2 (PMS2), and Homolog of MutS E. coli 6 (MSH6). However, mutations in MSH2 and MLH1 account for approximately 90% of HNPCC and service provision is generally based on analysis of only these two genes. Less than 1% of patients with HNPCC have mutations in the PMS2 gene.

Epidemiology in the Arab World

Lebanon
[See also: Syria > Farah et al., 2001]

Syria
Farah et al. (2001) discovered a Syrian “Cancer Family” residing in Lebanon by studying its pedigree. The father and the four siblings showed many features of Lynch syndrome I.
The father died at the age of 71 because of colon cancer. The index case was 41 years old when she became pregnant and presented a transverse colon tumor. Follow-up colonoscopy revealed a metachronous splenic fleure tumor. The eldest brother had an ascending colon carcinoma and presented symptoms of post-prandial crampy abdominal pain and distension. The other sibling died prior to the time of analysis. However, sigmoidoscopy with biopsies showed adenocarcinoma of the colon 8 cm from the anal verge. This tumor was not completely respectable because of adherence to the bony pelvis posteriorly. The fourth sibling was 50 years old and revealed three polyps which were removed. Two of the polyps showed mild to moderate dysplasia. The third polyp from the sigmoid colon had adenocarcinoma in situ with a free base and pedicle.

References

Contributors
Ghazi O. Tadmouri: 24.5.2006
Abeer Fareed: 24.5.2006