Heritable Gastrointestinal Cancer Syndromes

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KEYWORDS

• Gastrointestinal cancer • Genetics • Hereditary syndromes

KEY POINTS

- Although almost all gastrointestinal cancers develop as a consequence of sporadic genomic events, approximately 5% arise in the setting of germline mutations in genes known to be associated with cancer predisposition.
- The number of genes associated with heritable cancer syndromes continues to increase, and tumor phenotypes, along with family history, provide the framework for identifying individuals at risk.
- Making the diagnosis of a hereditary cancer syndrome has implications for management of patients with gastrointestinal neoplasia and for their family members.
- Systematic approaches that integrate family history and molecular characterization of tumors and polyps can facilitate identification of individuals with genetic predisposition to gastrointestinal cancer.

GENES AND CANCER

Like most other cancers, gastrointestinal neoplasms arise as a consequence of the deregulation of signaling pathways controlling cell survival and genome maintenance.[1] In almost all tumors, genetic mutations that affect the function of genes involved in key cell regulatory functions (eg, tumor suppression and DNA repair) occur sporadically in individual cells as so-called somatic events. However, a small proportion of individuals harbor mutations in their germline DNA that predispose to the development of gastrointestinal neoplasms. Because epithelial cells of the digestive tract are among the most rapidly dividing cells in the human body, germline mutations in a variety of cancer genes can be associated with dramatic increases in risk for gastrointestinal tumors.

Identification of the various heritable syndromes associated with risk for gastrointestinal neoplasia has come about through meticulous study of hundreds of individuals belonging to cancer families. Categorization of clinical histories and tumor phenotypes has led to the identification of specific hereditary cancer syndromes and the germline

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Table 1
Heritable cancer syndromes associated with predisposition to gastrointestinal cancers

Syndrome	Genes	Estimated Carrier Frequency (General Population)	Lifetime Cancer Risks						
			CRC	Gastric	Small Bowel	Pancreatic	Breast	Ovarian	Endometrial
Lynch Syndrome	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	1 in 280–350	[e]	[b]	—	[a]	[a]	[b]	[d]
Familial Adenomatous Polyposis	*APC*	1 in 1000	[e]	[a]	[b]	—	—	—	—
MUTYH-Associated Polyposis	*MUTYH*	1 in 100	[c]	—	—	—	—	—	—
Li Fraumeni Syndrome	P53	—	[b]	[b]		[a]	[c]	—	—
Juvenile Polyposis	SMAD4 BMPR1A	—	[c]	[b]		[a]	—	—	—
Peutz-Jeghers Syndrome	STK11	—	[c]	[b]	[a]	[c]	[d]	—	—
Cowden or PTEN Hamartoma Tumor Syndrome	PTEN	—	[b]	—	—	—	[c]	—	[c]
Hereditary Diffuse Gastric Cancer	CDH1	—	[a,b]	[e]	—	—	[d]	—	—
Hereditary Breast Ovarian Cancer Syndrome	BRCA1 BRCA2 PALB2	—	—	—	—	[a] TBD	[e] [c]	[c] [a]	—
Familial Atypical Multiple Mole Melanoma	CDKN2A	—	—	—	—	[b]	—	—	—

Abbreviation: TBD, to be determined.
[a] 2% to 5%.
[b] 5% to 20%.
[c] 21% to 40%.
[d] 41% to 60%.
[e] Greater than 60%.
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