How can histopathologists help clinical genetics in the investigation of suspected hereditary gastrointestinal cancer?

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Abstract

Histopathologists are critical in the diagnosis of hereditary gastrointestinal tumours. This is increasingly important as genetic testing becomes more available and the benefits of anti-cancer surveillance in those at increased risk are realised. Cancer genetics services should include pathologists and be organised on multidisciplinary team lines. Hereditary cancer syndromes predispose to tumours throughout the GI tract. Lynch syndrome is the most prevalent hereditary GI cancer condition, responsible for ~3.3% of all colorectal as well as other GI and extra-intestinal cancers. Tumour tests to diagnose Lynch syndrome are important in guiding genetic testing, and can be used systematically to screen cancers for the condition. Familial adenomatous polyposis and all the other forms of hereditary polyposis put together account for <1% of all colorectal cancer. However, the histological distinction of the various polyposes, including type, site and numbers of polyps is crucial in informing genetic testing.

Keywords Polyposis; Cowden syndrome; DNA mismatch repair; gastrointestinal neoplasms; genetic predisposition to disease; immunohistochemistry; juvenile polyposis syndrome; Lynch syndrome; microsatellite instability; Peutz-Jeghers syndrome

Context

A fundamental part of the clinical and laboratory examination of a patient with a gastrointestinal tumour is the histopathology. It is absolutely critical in achieving the diagnosis. This is especially the case where that diagnosis includes a possible hereditary predisposition, because this has implications for both the patient, the relatives, and unrelated individuals who happen to have the same underlying genetic mutation.

Phenotype is defined as "*the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment*" and, therefore, is what you are: a function of your genes and the environment they find themselves in. Histopathology is therefore crucial in defining an individual tumour phenotype, informing in turn genetic investigations and the interpretation of genetic variation found in that patient. The genome, an individual's complete DNA sequence, is now accessible. About one quarter of all the 21,000 or so human genes have an associated clinical phenotype. The protein-coding parts of all genes, constituting about 2% of the genome, is called the exome, and clinical testing of the exome is already available. Hence, as medicine moves from a genetic, single gene, era into the genomic era, so it becomes increasingly important to define phenotype. Dysmorphism, that is abnormalities in gross morphologic development, is an important feature of many genetic conditions and why clinical geneticists are highly trained in recognising such features. While some cancer genetic conditions certainly do have associated dysmorphic features, the histopathologist can be thought of as the cancer geneticist's dysmorphologist — histopathologists having the necessary expertise, skills and tools to define abnormalities in tumours at the macroscopic, microscopic and molecular level, working where necessary with colleagues in related disciplines.

Cancer genetics now accounts for more than half of all the clinical genetics care provided in the UK, and the role of histopathology in the provision of such services is thus proportionately important. We would strongly urge colleagues in genetics, both clinical and laboratory, to work closely with histopathologists, and vice versa: the model of the multidisciplinary team will be familiar as best practice. The importance of critically utilizing key information in pathology reports is stressed to those who attend e.g. the UK national cancer genetics courses for doctors, counselors and laboratory scientists, as is asking for histopathological review of multiple samples from family members in complex cases. However, whilst the mainstay of clinical cancer genetics has classically been the 'family history', it is becoming apparent that laboratory tests on tumours have better specificity and sensitivity than family history at finding those who harbour inherited mutations. So, as such tests become cheaper to perform, the identification of patients with hereditary predisposition is moving towards systematic screening for biomarkers in incident cases.

Cancer genetic conditions generally predispose to tumours of various types and at more than one site. Whilst histopathologists will usually be presented with tissue from a specific organ, we have decided to take a condition rather than organ-based approach and concentrate on those conditions which are relatively common or warrant careful differentiation on histological grounds.

It should be borne in mind that many syndromes are multisystem and predispose to more than just gastrointestinal (GI) tumours. Also, that this review is not exhaustive and does not need to be, as nowadays there are many online sources of information regarding hereditary cancer, such as the family cancer database (FaCD: http://www.familialcancerdatabase.nl/). Here,

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the features of known syndromes may be browsed, help can be given with identifying a syndrome from tumour types and symptoms, or searches on a word or gene can be performed. We recommend that the reader refer to the relevant sections of this resource in conjunction with this review. Online Mendelian Inheritance in Man (OMIM; http://www.omim.org/) is another valuable resource: for each gene and phenotype there are OMIM entries. The *Oxford Desk Reference: Clinical Genetics* has sections on GI cancer and associated syndromes.[1]

GI-cancer associated genetic conditions

These can be divided into polyposes, in which an excess of polyps is seen, and those in which there is no obvious excess, such as Lynch syndrome and hereditary diffuse gastric cancer.

Lynch syndrome

Lynch syndrome (LS) is the most prevalent single-gene disorder predisposing to colorectal cancer. It is caused by constitutional mutations affecting one of four DNA mismatch repair (MMR) genes, specifically *MSH2, MLH1, MSH6* or *PMS2*. In Denmark, where systematic testing for LS is now carried out on all CRC, approximately 3.3% are now known to be due to LS, implying a prevalence of at least 1:500. The main cancers LS predisposes to are CRC and endometrial cancer, but a wide spectrum of associated tumours is now recognised, including from the GI tract, stomach, small bowel, hepatobiliary tract and, possibly, pancreatic cancer, but also upper urinary tract, ovaries, brain, prostate and breast.[2] The average age of onset of CRC is approximately 42 y, but varies with the underlying gene, as does the spectrum of associated cancers. An individual with LS has a high, but not inevitable risk of cancer. Current best estimates of risk in mutation carriers to age 70 y of any LS-associated cancer are ~60% in men and ~70% in women. Both *MSH2* and *MLH1* are associated with higher risks and younger onset, with *MSH6* and *PMS2* conferring lower risks and at older age, while *MSH6* confers a relatively greater risk of endometrial cancer (Table 1).[2,3]

In the case of *MSH2* there is an additional mechanism of disease in that large deletions in an adjacent gene, *EPCAM* (whose product is expressed in gut mucosal brush border) can affect MSH2 expression in one of two ways. With deletions encompassing both *EPCAM* and *MSH2* the associated phenotype is indistinguishable from mutations of any sort involving *MSH2* alone. However, deletions only involving *EPCAM* can lead to read through of mRNA into *MSH2*, resulting in expression of a non-functional protein and methylation of the *MSH2* promoter, which prevents any normal MSH2 being produced. Curiously, the associated phenotype is of both large and small bowel cancers, but not endometrial cancer, which may reflect the tissue expression pattern of EPCAM.

Because of the tendency in LS to earlier onset and somewhat more survivable cancers, some individuals can and often do develop two or more cancers. The variety of associated tumour types also means that a possible diagnosis of LS may not be immediately obvious to clinicians (or patients) either in an individual or family. Hence, it is important for the pathologist to be aware of such possible combinations and alert colleagues to them, if necessary after appropriate investigation and discussion within an MDT that includes cancer genetics input.

The cells of individuals with LS have proficient DNA mismatch repair (MMR), but if a somatic mutation occurs in the other copy of the respective gene then MMR deficiency results in that cell. One consequence of this is that the genome of such cells starts to accumulate innumerable small mutations, particularly, but by no means exclusively in repetitive stretches of DNA, called microsatellites, resulting in the phenomenon of microsatellite instability (MSI). Another is that the loss of MMR function is manifest as abnormal or lost expression of the affected MMR protein (and often its binding partner), readily detectable by immunohistochemistry (IHC). Concomitantly, and probably because MMR is necessary for chromosomal recombination to occur, such cells then stop accumulating large scale chromosomal defects, classically manifest as chromosomal instability, classically typified by loss of heterozygosity (LOH). Hence, tumours which have lost MMR not only have MSI and usually abnormal MMR expression, but are typically near-diploid.

It has been suggested that the raised mutation rate in MMR deficient cells is the Darwinian selectable advantage driving such tumours. However, while the phenomenon of MSI is certainly diagnostically useful there is good reason to believe that it may just be a paraphenomenon: that the mutation rate in cells is not limiting and that it is a reduction in MMR-triggered apoptosis which is the driver. It is also suggested that the CRC in LS develop much faster than in the general population, with the high frequency of interval cancers despite frequent (2 yearly) colonoscopy being cited as evidence. However, this presupposes that such cancers all arise in adenomas and the role of the serrated lesion in LS may be more significant than has been previously recognised.

Muir-Torre syndrome and LS: Muir-Torre syndrome (MTS) is the occurrence in the same individual of keratoacanthomas or sebaceous adenomas/carcinomas with an internal cancer and is common in LS, more often, but not exclusively associated with

Major cancer risks in Lynch syndrome by age 70y, by underlying gene

	MSH2	*MLH1*	*MSH6*	*PMS2*
Colorectal cancer (males)	57%	34%	22%	19%
Colorectal cancer (females)	38%	38%	10%	11%
Endometrial cancer (females)	30%	18%	26%	12%

Refs.[2,3].

Table 1

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