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MSH6 syndrome

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The *MSH6* gene in collaboration with *MSH2*, *MLH1*, *MSH3*, *PMS1* and *PMS2* genes is involved in one of the systems repairing the errors that arise during DNA replication, called the "methyl directed mismatch repair" system [1-3]. *hMLH1* and *hMSH2* mutations give rise most frequently to the classical Lynch syndrome (HNPCC) [4-6]. *hMSH6* mutations often occur in clinically less typical HNPCC families, that do not fulfil the Amsterdam criteria [7-11]. So far more than 200 families with germline *hMSH6* mutation have been described (www.med.ca/MMRvariants).

Characteristic features of families with *hMSH6* mutation are:

- higher risk for colorectal cancer (~70% for men and ~30% for females), endometrial cancer (~70%) and also for ovarian, upper urinary tract, stomach and breast cancer [12],
- higher incidence of extracolonic cancers, when compared with HNPCC families [13],
- later age at onset of cancers, e.g. for colorectal cancer the mean age at diagnosis is ~56 years, for endometrial cancer ~54 years and for ovarian cancer ~49 years [12, 13],
- frequent left-sided localization of colorectal cancer [9].

The prevalence of *hMSH6* constitutional mutations in families that fulfil the Amsterdam criteria is about 5-10% [8, 9].

Because the frequency of *hMSH6* mutations in other groups is not precisely determined, we recommend the following diagnostic procedure for *hMSH6* mutation detection:

- selection of families with colorectal, endometrial, ovarian, urinary tract and/or stomach, breast cancer aggregation,
- immunohistochemical analysis (IHC) of *hMSH6* protein expression in tumour colorectal or endometrial tissue [14-16],
- in cases of hMSH6-negative tumours, DHPLC/ sequencing of the coding regions of the *hMSH6* gene.

Among the reported *hMSH6* mutations about 30 are recurrent, i.e. they are detected in more than one family [17-19]. Probably in the near future diagnostic tests will be described to allow cheap, simple and fast detection of mutations showing a "founder effect" characteristic for particular ethnic groups.

Surveillance protocol

As yet a suitable surveillance programme in *hMSH6* families based on prospective family trials is not available. In our centre we offer the following surveillance protocol:

- colorectal cancer – colonoscopy every 2 to 3 years beginning at least 15 years before the earliest age of onset in the family,
- endometrial cancer – annual transvaginal ultrasound scan starting at least 15 years before the earliest age of onset in the family,
- screening for other cancers depending on the tumour spectrum in the family.

Surgical management

Because of the described higher risk of developing multiple (synchronous and metachronous) cancers and also endometrial cancer in females after age of 50 years in *hMSH6* mutation carriers [12, 17, 20], it is recommended to take into consideration surgical treatment similar to that for patients with CRC associated with Lynch syndrome, i.e. colectomy with ileorectal anastomosis, extended by prophylactic hysterectomy and oophorectomy for women over 50 years old.

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